ARNOLD & PORTER LLP

Zhiqiang "Zack" Zhao, Ph.D.
Zhiqiang_Zhao@aporter.com

202.942.5055
202.942.5999 Fax

555 Twelfth Street, NW
Washington, DC 20004-1206

March 13, 2006

PUBLIC VERSION

Via Hand Delivery

The Honorable Marilyn R. Abbott
Secretary
U.S. International Trade Commission
500 E Street, S.W.
Washington, D.C. 20435

Re: In the Matter of CERTAIN RUBBER ANTIDEGRADANTS, COMPONENTS THEREOF, AND PRODUCTS CONTAINING SAME; Inv. No. 337-TA-533

Dear Secretary Abbott:

Enclosed for filing in the above-referenced investigation is the Public Version of the Petition for Review of Respondents Sinorgchem Co., Shandong and Sovereign Chemical Company of the Administrative Law Judge's February 17, 2006 Final Initial and Recommended Determinations.

Sinorgchem Co., Shandong's confidential business information has been redacted pursuant to 19 C.F.R. § 210.04(f)(3)(ii).

Please call the undersigned should you have any questions. Thank you for your assistance in this matter.

Sincerely,

Zhiqiang Zhao

Counsel for Respondent
Sinorgchem Co., Shandong

Enclosure

CERTIFICATE OF SERVICE

I hereby certify that copies of the foregoing Public Version of the Petition for Review of Respondents Sinorgchem Co., Shandong and Sovereign Chemical Company of February 17, 2006 Final Initial and Recommended Determinations were served upon the following parties as indicated on this 13th day of March, 2006.

VIA HAND DELIVERY

Hon. Marilyn R. Abbott (1 Orig + 14 copies)
Office of the Secretary
U.S. International Trade Commission
500 E Street, S.W.
Washington, D.C. 20436
(HAND DELIVERY ONLY)

Juan Cockburn, Esq.
Office of Unfair Import Investigations
U.S. International Trade Commission
500 E Street, S.W., Suite 401
Washington, D.C. 20436
juan.cockburn@usitc.gov

V. James Adduci II
Adduci, Mastriani & Schaumberg, LLP
1200 Seventeenth Street, N.W.
Washington, DC 20036
Tel: (202) 467-6300
Fax: (202) 466-2006
Counsel for Korea Kumho Petrochemical Co., Ltd.
browne@adduci.com
szebrat@adduci.com

Gregory C. Dorris
Pepper Hamilton LLP
Hamilton Square
600 Fourteenth Street, N.W.
Washington, D.C. 20005-2004
Tel: (202) 220-1224
Fax: (202) 20-1665
Counsel for Flexsys America, L.P.
dorrisg@pepperlaw.com
carpenterc@pepperlaw.com

James K. Kearney
Womble Carlyle Sandridge & Rice
Seventh Floor
1401 I Street, N.W.
Washington, DC 20005
Tel: (202) 467-6900
Fax: (703) 918-2269
Counsel for Sovereign Chemical Company
jkearney@wcsr.com

VIA FEDERAL EXPRESS

Eric C. Cohen
Katten Muchin Zavis Rosenman
525 West Monroe Street, Suite 1600
Chicago, Illinois 60661-3693
Tel: (312) 902-5200
Fax: (312) 902-5648
Counsel for Flexsys America, L.P.
eric.cohen@kmzr.com
charles.krikorian@kmzr.com
carolyn.miller@kmzr.com

Nanda K. Alapati
Womble Carlyle Sandridge & Rice LLP
8065 Leesburg Pike, 4th Floor
Tysons Corner, VA 22182-2738
Tel: (703) 394-2216
Fax: (703) 790-2623
Counsel for Sovereign Chemical Company
Nalapati@wcsr.com

Deborah A. Coleman
Hahn Loeser & Parks LLP
3300 BP Tower
200 Public Square
Cleveland, Ohio 44114
Tel: (216) 274-2220
Fax: (216) 241-2824
Counsel for Sovereign Chemical Company
dacoleman@hahnlaw.com
jcunniff@hahnlaw.com

Scott M. Oldham
Hahn Loeser & Parks LLP
One GOJO Plaza, Suite 300
501 S. Main Street
Akron, OH 44311-1076
Tel: (330) 864-5550
Fax: (330) 864-7986
Counsel for Sovereign Chemical Company

Robert G. Badal
Edward J. Slizewski
Heller Ehrman LLP
601 South Figueroa Street, 40th Floor
Los Angeles, CA 90017
Tel: (213) 689-7645
Fax: (213) 614-1868
Counsel for Korea Kumho Petrochemical Co., Ltd.
robert.badal@hellerehrman.com

William J. Bohler
Guy W. Chambers
Byron W. Cooper
Mark T. Jansen
Maureen Sheehy
Townsend and Townsend and Crew
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111
Tel: (415) 576-0200
Fax: (415) 576-0300
Counsel for Korea Kumho Petrochemical Co., Ltd.
masheehy@townsend.com

Gary Ropski
Brinks, Hofer, Gilson & Lione
NBC Tower
455 North Cityfront Plaza
Suite 3600
Chicago, Illinois 60611
Tel: (312) 321-4200
Fax: (312) 321-4299
Counsel for Flexsys America, L.P.
gropski@usebrinks.com

Alan H. Blankenheimer
Heller Ehrman LLP
4350 La Jolla Village Drive, 7th Floor
San Diego, CA 92122
Tel: (858) 450-5817
Fax: (858) 450-8499
Counsel for Korea Kumho Petrochemical Co., Ltd.
alan.blankenheimer@hellerehrman.com

Tiana Butcher
Legal Assistant

PUBLIC VERSION

UNITED STATES INTERNATIONAL TRADE COMMISSION
WASHINGTON, D.C.

Before the Honorable Paul J. Luckern

In the Matter of CERTAIN RUBBER ANTIDEGRADANTS, COMPONENTS THEREOF, AND PRODUCTS CONTAINING SAME	Investigation No. 337-TA-533

PETITION FOR REVIEW OF RESPONDENTS SINORGCHEM CO., SHANDONG AND SOVEREIGN CHEMICAL COMPANY OF FEBRUARY 17, 2006 FINAL INITIAL AND RECOMMENDED DETERMINATIONS

Marcia H. Sundeen
1700 Pennsylvania Avenue, N.W. Suite 400
Washington, DC 20006
Telephone: (202) 349-3673

Stanton T. Lawrence, III
Paul J. Zegger
Zhiqiang Zhao
Arnold & Porter LLP
555 Twelfth Street, NW
Washington, DC 20004
Telephone: (202) 942-5060

Jiabin Wang
Shanlon Wu
King and Wood PRC Lawyers
31st Floor, Tower A, Jianwai SOHO,
39 Dongsanhuan Zhonglu
Chaoyang District, Beijing 100022
People's Republic of China

Manni Li
Venable LLP
575 7th Street, NW
Washington, DC 20004
Telephone: (202) 344-8119

Counsel for Sinorgchem Co., Shandong

James K. Kearney
Womble Carlyle Sandridge & Rice LLP
1401 I Street, N.W., 7th Floor
Washington, DC 20005
Telephone: (202) 857-4400

Deborah A. Coleman
Hahn Loeser & Parks LLP
3300 BP Tower
200 Public Square
Cleveland, Ohio 44114
Telephone: (216) 621-0150

Scott M. Oldham
John J. Cunniff
Hahn Loeser & Parks LLP
One GOJO Plaza, Suite 300
501 S. Main Street
Akron, Ohio 44311
Telephone: (330) 864-5550

Nanda K. Alapati
Womble Carlyle Sandridge & Rice LLP
8065 Leesburg Pike, 4th Floor
Tysons Corner, Virginia 22182
Telephone: (703) 790-3310

Counsel for Sovereign Chemical Company

Dated March 13, 2006

ABBREVIATIONS

Parties

Official Name	Short Form
Flexsys America L.P.	Flexsys or Complainant
Korea Kumho Petrochemical Co., Ltd.	KKPC
Sinorgchem Co., Shandong	Sinorgchem
Sovereign Chemical Company	Sovereign
Commission Investigative Attorney	ITC Staff
Administrative Law Judge	ALJ

Patents In Suit

Official Name	Short Form
U.S. Patent No. 5,117,063	'063 patent
U.S. Patent No. 5,608,111	'111 patent

Technical Terms

Term	Short Form
N-(l,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine	6PPD
N-phenyl-p-phenylenediamine, 4-aminodiphenylamine	4-ADPA or PADA
4-nitrosodiphenylamine	p-NDPA or 4-NODPA
4-nitrodiphenylamine	4-NDPA
Tetramethylammonium hydroxide	TMAH

Other Abbreviations

Term	Abbreviation
Initial and Recommended Determinations	ID
Hearing Transcript	Tr.

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I. INTRODUCTION

Pursuant to Commission Rule 210.43(b), 19 C.F.R. 210.43(b), Respondents Sinorgchem Co., Shandong ("Sinorgchem") and Sovereign Chemical Company ("Sovereign") petition for review of the issues specified below that were decided in the Initial and Recommended Determinations ("ID") of the Hon. Paul J. Luckern, dated February 17, 2006.

A. Background

This case involves antidegradant chemicals, which have been known and used for many years as additives in tires and other rubber products. Flexsys asserted infringement of two process patents, the '063 patent and its continuation-in-part, the '111 patent. The '111 patent claims benefit under 35 U.S.C. § 119 to the filing date of the '063 patent. Copies of the '063 and '111 patents are attached hereto as Exhibits 1 and 2, respectively. These patents relate to a process for the manufacture of the antidegradant referred to as "6PPD," a precursor chemical called "4-ADPA"[1] (4-aminodiphenylamine), and 4-ADPA intermediates.[2] The Flexsys patents are directed to a purported improvement on an admittedly old chemical reaction described in literature dating back to 1903 describing the reaction of aniline and nitrobenzene in the presence of a base to form a 4-ADPA intermediate.

The ALJ issued his ID on February 17, 2006. In the ID, contrary to the position of the ITC staff, the ALJ found that the Complainant had established that a violation of Section 337 exists with respect to Sinorgchem and Sovereign in the importation into the United States, sale for importation, or the sale within the United States after importation of 4-ADPA and 6PPD, in

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[1] Both 6PPD and 4-ADPA have been known and used in industry for many years.

[2] These intermediates are 4-nitrosodiphenylamine ("4-NODPA") and 4-nitrodiphenylamine ("4-NDPA"), and have also been known for many years. *See e.g.*, Ex. 1, '063 patent, col. 1, lines 23-35, 62-68.

violation of claims 30 and 61 of the '063 patent and claims 7 and 11 of the '111 patent. He also found that a domestic industry exists that practices the asserted claims. The ALJ further determined that the '063 and '111 patents are not invalid. The ID recommended that a limited exclusion order be directed to each of Sinorgchem and Sovereign regarding accused 4-ADPA and 6PPD made by Sinorgchem. As the ALJ noted, Flexsys is not seeking relief against downstream products (SX-6), and he recommended that no bond be imposed during the 60-day Presidential review period.

The ID contains a number of errors of law and fact listed below. Respondents Sinorgchem and Sovereign respectfully seek Commission review and reversal of the following errors.

(i) The ID sets forth a legally incorrect and incomplete claim construction of the defined term "controlled amount";

(ii) The ID incorrectly finds that Sinorgchem and Sovereign infringe the asserted claims;

(iii) The ID fails to conclude that the asserted claims are invalid for not satisfying the requirements of 35 U.S.C. § 112, ¶ 2, *i.e.,* "indefiniteness";

(iv) The ID fails to conclude that the asserted claims are invalid for obviousness based on the requirements of 35 U.S.C. § 103; and

(v) The ID incorrectly concludes that Flexsys has established the technical prong of the domestic industry requirement.

B. The Standard of Review

Commission Rule 210.43(b)(1) specifies that review may be sought on an issue decided in an ID on one or more of the following grounds:

(i) That a finding or conclusion of material fact is clearly erroneous;

(ii) That a legal conclusion is erroneous, without governing precedent, rule or law, or constitutes an abuse of discretion; or

(iii) That the determination is one affecting Commission policy.

19 C.F.R. 210.43(b)(1). As detailed in this Petition, the ALJ failed to apply properly established patent law on claim construction, found infringement and the existence of a domestic industry based on an erroneous claim construction, and failed to apply properly the law of the Federal Circuit on patent invalidity for indefiniteness and obviousness. Contrary to the ID of the ALJ, the ITC staff supported Respondents on claim construction, noninfringement, lack of a domestic industry, and invalidity for indefiniteness.

II. THE '063 AND '111 PATENTS AND THE PRIOR ART WOHL PAPER

Numerous methods of making 4-ADPA and 6PPD have been known for years. (*See, e.g.*, Ex. 1, '063 patent, col. 1, lines 23-61.) Generally, the '063 and '111 patents describe a method for producing 4-ADPA intermediates and 4-ADPA by reacting or coupling aniline and nitrobenzene with a "suitable solvent" and a "suitable base" under conditions using a *"controlled amount" of protic material (e.g., water)*. Flexsys has asserted claims 30 and 61 of the '063 patent and claims 7 and 11 of the '111 patent ("the asserted claims"). All of the asserted claims include the limitation "controlled amount" of protic material, and that claim limitation is the subject of this dispute. Claim 30 of the '063 patent is exemplary and reads as follows:

> A method of producing 4-aminodiphenylamine (4-ADPA) comprising the steps of: a) bringing aniline and nitrobenzene into reactive contact in a suitable solvent system; b) reacting the aniline and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and *controlled amount* of protic material to produce one or more 4-ADPA

> intermediates; and c) reducing the 4-ADPA intermediates under conditions which produce 4-ADPA.[3]

All of the asserted claims require that a "controlled amount" of protic material during the reaction of aniline and nitrobenzene in the presence of a suitable base and a suitable solvent. The patentees emphasized in the specification and the prosecution history that this was an important feature of the process described and claimed in the patents. (Ex. 1, '063 patent, col. 4, lines 31-32 and col. 9, lines 20-21; Ex. 2, '111 patent, col. 5, lines 27-28 and col. 10, lines 30-31.) The '063 patent includes Examples 1 to 12; the '111 patent, a later-filed continuation-in-part, adds Examples 13 to 21.

A. Flexsys Did Not Invent Either The Known Three-Step Commercial Process To Make 6PPD Or The Reaction Of Aniline, Nitrobenzene, And Base

It was undisputed that various three-step commercial processes for making 6PPD were known for many decades prior to 1990. Many of those processes made 4-ADPA and 6PPD by (1) reacting p-*chloro*nitrobenzene ("PCNB") with aniline to form 4-ADPA intermediates, followed by (2) the reduction thereof to 4-ADPA, and then (3) alkylation of 4-ADPA to 6PPD.[4] Those processes produced chlorine-containing by-products that in 1990 had been recognized as being environmentally unacceptable. The only arguably novel step in the asserted claims, compared to the known commercial processes to make 4-ADPA and 6PPD, was the use of the reaction of aniline with nitrobenzene, rather than with p-*chloro*nitrobenzene, in the presence of a base, to form the 4-ADPA intermediates in steps (a) and (b) of the asserted claims of the '063 and '111 patents. That chlorine-free step is what Wohl clearly teaches. And, it was clearly

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[3] Unless otherwise indicated, all emphasis is added.

[4] Step (1) corresponds to steps (a) and (b) of the asserted claims; step (2) corresponds to step (c) of the asserted claims; and step (3) corresponds to step (d) of asserted claim 61 of the '063 patent and asserted claim 11 of the '111 patent.

recognized by Monsanto that Wohl disclosed long before 1990 to react aniline and nitrobenzene with base to produce 4-ADPA intermediates. (Ex. 3, Preliminary Amendment to '111 Application, corresponding to CX-4, at FA030986.) Because of the new motivation in 1990 to eliminate chlorine from the three-step Monsanto commercial process for making 6PPD for environmental purposes, it was clearly obvious to use Wohl's chlorine-free process in place of conventional step (1). Contrary to the apparent misunderstanding of the ALJ (ID at 8-33 and 110-13), the 1903 Wohl prior art reference does disclose reacting aniline and nitrobenzene in the presence of a base and excess aniline as the solvent to produce a 4-ADPA intermediate. (Ex. 18, RX-9, Wohl publication.) There was water present in the Wohl system that was formed as a reaction product of the coupling reaction of aniline and nitrobenzene. (ID at 23-24; CX-30.) Wohl conducted the reaction at a temperature of 120°C. The result of that condition was that Wohl controlled the amount of protic material, *i.e.*, water, formed and present during the course of his reaction by continuous distillation during the reaction. Another result of that removal of water by distillation was to increase the yield of 4-ADPA intermediates according to the Law of Mass Action (also referred to as Le Chatelier's Principle). (Ex. 4, Tr. 1960:18-1961:18.)[5]

Moreover and importantly, Flexsys expressly acknowledged during prosecution that Wohl disclosed reacting aniline and nitrobenzene with a base (sodium hydroxide) to produce the same 4-ADPA intermediate as claimed by Flexsys. Flexsys made clear during the prosecution of the applications for the '063 and '111 patents that Wohl discloses "the reaction of aniline with nitrobenzene in aniline as solvent using NaOH as base under 'anhydrous' conditions," and identifies "the minor product of this reaction of aniline with nitrobenzene as p-

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[5] All hearing transcript pages cited in this Petition for Review are collected in Ex. 4.

nitrosodiphenylamine (p-NDPA). (Ex. 3, corresponding to CX-4, at 111-083.) That statement made during prosecution to the United States Patent and Trademark Office ("USPTO") is an admission binding on Flexsys, but ignored entirely by the ALJ in the ID.

Tellingly, the European Patent Office ("EPO") has considered whether the Wohl 1903 publication describes steps (a) and (b) of the asserted claims of the '063 and '111 patents and found that Wohl by itself discloses all aspects of those claim steps. On that point, the EPO revoked claim 1 of Flexsys' corresponding European Patent No. 0590053 based on the Wohl 1903 publication (referred to by the EPO as reference E1). (Ex. 5, corresponding to RX-835, at FA008914-17.) Also, the Korean courts have reached the same conclusion – the Wohl 1903 paper describes the claim steps (a) and (b) in the Flexsys' Korean patent corresponding to the '063 patent. (Ex. 6, corresponding to RX-847, at 09135T and 09148T; Ex. 7, corresponding to RX-848, at 09159T and 09168T.) These decisions were before the ALJ, but were ignored in their entirety in the ID.

There is also clear evidence in the record that the Wohl 1903 publication was appreciated by independent, unbiased academics in the field of synthetic organic chemistry as the recognized and preferred route to synthesize 4-NODPA, a 4-ADPA intermediate, by Flexsys' claim definition. In 1992, a Chinese academic from the Beijing Institute of Technology published the *Manual of Organic Synthesis* which describes the development and application of "classical organic synthetic reactions" for over 1700 commonly used organic compounds. (Ex. 8 at SCS014061.) That *Manual*, written by an independent author reviewing the field, appreciated that Welcher reported in 1947 that the Wohl 1903 synthesis was the recognized and preferred route to 4-nitrosodiphenylamine. Indeed in 1947, Welcher described in an academic review methods for making various organic reagents. Welcher reported that a known method to

synthesize p-nitrosodiphenylamine (another name for 4-NODPA) was by reacting aniline and nitrobenzene with a base and clearly referenced the Wohl 1903 publication (in footnote 1) as the source of that synthesis. (Ex. 8, corresponding to RX-857 at SCS014062-63.)[6] (Ex. 8 at SCS014062-63.) Again, this public and independent evidence was ignored by the ALJ in the ID.

The inescapable conclusion from this evidence, *all* ignored by the ALJ, is that, contrary to the implications of the ALJ, the direct reaction of aniline and nitrobenzene in the presence of a base to produce 4-ADPA intermediates, while controlling the amount of water present during the reaction, was *not* invented by Flexsys, but rather was discovered and described by Wohl. Moreover, this conclusion has been recognized on numerous occasions by independent and unbiased academics and foreign patent tribunals. Flexsys did not invent the reaction of aniline and nitrobenzene with base to produce a 4-ADPA intermediate. To replace conventional steps (1) in the known commercial process with the chlorine-free Wohl reaction would have been obvious in 1990, particularly given the new motivation for a chlorine-free, environmentally acceptable process at Monsanto.

Flexsys purported to distinguish its claimed process from the prior art Wohl process by emphasizing the importance of controlling the amount of protic material, particularly water, in the coupling reaction. *See, e.g.*, Ex. 1, '063 patent, col. 2, lines 23-25. Again, in the prosecution history of the '111 patent, the patentees asserted that "controlling the amount of protic material" was the *key distinguishing feature* of the claims from the prior art. However, as previously noted, Wohl discloses reacting aniline and nitrobenzene in the presence of a base to produce the

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[6] Ex. 9, corresponding to RX-857A, is a copy of the pertinent pages of Welcher; that exhibit, improperly excluded from evidence by the ALJ is relied on only to confirm that SCS014063 in Ex. 8 is indeed a copy of pages 406-07 of the 1947 Welcher text (Ex. 8 at SCS014063).

claimed 4-ADPA intermediate, while controlling the amount of water present during the reaction. In distinguishing Wohl during prosecution, Flexsys argued that "[i]t was applicants who discovered the criticality of controlling the amount of protic material present in the reaction of aniline and/or substituted aniline derivatives with nitrobenzene." (Ex. 3, Preliminary Amendment for '111 application, at 7.) This argument was not a fair and proper distinction of the teachings of Wohl as understood by others, particularly in the academic publications (Ex. 8) and by both the EPO (Ex. 5) and the Korean courts (Exs. 6 and 7).

B. Flexsys Defined A "Controlled Amount" Of Protic Material

In the specifications of both patents, Flexsys defined exactly what it meant by the claim term" controlled amount" of protic material. (Ex. 1, col. 4, lines 31-60; Ex. 2, col. 5, lines 27-55.) Specifically, *when aniline is used as the solvent, a "controlled amount" of protic material requires that the amount of water be no higher than about 4% based on the volume of the reaction mixture*. (Ex. 1, col. 4, lines 58-60; Ex. 2, col. 5, lines 52-55.) This definition was in the application for the '063 patent as filed and was not changed when the continuation-in-part application for the '111 patent was filed four years later.

Throughout both specifications, the inventors consistently taught that when aniline is the solvent, the amount of water in the reaction mixture could be no more than about 4% or the reaction would be unacceptable. In the Detailed Description of the Invention, the inventors stated:

> Generally, when the reaction is conducted in aniline, water present in the reaction in an amount greater than about 4% (based on volume of the reaction mixture) inhibits the reaction of the nitrobenzene to an extent where the reaction is no longer significant. *Reducing the amount of water to below the 4% level causes the reaction to proceed in an acceptable manner.*

(Ex. 1, col. 4, lines 32-39; Ex. 2, col. 5, lines 28-34.) Equally significant, the patentees put the key term in quotes and defined that the upper limit of protic material is about 4% when aniline is the solvent:

> A "*controlled amount*" of protic material is an amount up to that which inhibits the reaction of aniline with nitrobenzene, *e.g.*, *up to about 4% H_2O based on the volume of the reaction mixture when aniline is utilized as the solvent* . . . . When aniline is utilized as a solvent with the same base [TMAH], the upper limit is 4% based on the volume of the reaction mixture.

(Ex. 1, col. 4, lines 48-52 and 58-60; Ex. 2, col. 5, lines 47-47 and 52-55.) The patentees specifically defined and delineated what is meant by controlling the amount of protic material (*e.g.*, water) in a specific solvent system, *i.e.*, aniline. These clear and deliberate statements throughout the specifications of both the '063 and the '111 patents explicitly defined a "controlled amount" of protic material in the context of the claimed process.

III. SINORGCHEM'S PROCESS

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IV. THE ALJ's DETERMINATION ON CLAIM CONSTRUCTION IS WRONG

The issue of claim construction is a question of law. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996). The central issue

of claim construction in this Investigation is the meaning of the claim term "controlled amount" of protic material, which appears in all four claims at issue. The ALJ accepted Flexsys' construction of this term to mean that:

> the amount of protic material (which is not limited to water) should be controlled between (1) an upper limit of protic material which is the amount of protic material beyond which the reaction between nitrobenzene and aniline (or substituted aniline) is inhibited and (2) a lower limit of protic material which is the amount of protic material below which the desired selectivity for 4-ADPA intermediates is not maintained.

(ID at 78-79.) Putting aside whether this definition is correct for solvent systems other than aniline, the definition is legally incorrect and incomplete when applied to processes in which aniline is used as the solvent and water is the protic material.

A. The ALJ Incorrectly Ignored The Express Definition Of The Claim Term "Controlled Amount" When Aniline Is The Solvent

When aniline is the solvent, the '063 and '111 patentees adopted an express definition for "controlled amount" of protic material, limiting the maximum amount of water to "about 4%." In fact, the patentees explained this definition several times, culminating in an express definition of the claim language in quotations. The patentees first explained the danger of exceeding 4% water, when aniline is the solvent:

> Generally, when the reaction is conducted in aniline, water present in the reaction in an amount greater than about 4% H_2O, (based on volume of the reaction mixture) inhibits the reaction of the aniline with the nitrobenzene to an extent where the reaction is no longer significant.

(Ex. 1, col. 4, lines 32-37; Ex. 2, col. 5, lines 28-33.) The patentees then explained further that, for the claimed reaction to even proceed in an acceptable manner, the amount of water should be reduced to below 4%, stating that: "reducing the amount of water to below the 4% level causes

the reaction to proceed in an acceptable manner." (Ex. 1, col. 4, lines 37-39; Ex. 2, col. 5, lines 33-34.)

A few sentences later, the patentees, using quotation marks, expressly defined "controlled amount" of protic material (*e.g.*, water) *when aniline is the solvent* as less than about 4% water:

> a *"controlled amount"* of protic material is an amount up to that which inhibits the reaction of aniline with nitrobenzene, *e.g.*, *up to about 4% H_2O based on volume of the reaction mixture when aniline is utilized as the solvent* . . . When aniline is utilized as a solvent with the same base [TMAH], *the upper limit is 4% H_2O* based on the volume of the reaction mixture.

(Ex. 1, col. 4, lines 48-52 and 58-60; Ex. 2, col. 5, lines 43-47 and 52-55.) The patentees' deliberate use of quotations around the claim term is an explicit definition. *Durel Corp. v. Osram Sylvania Inc.*, 256 F.3d 1298, 1301 (Fed. Cir. 2001); *Cultor Corp. v. A.E. Staley Mfg. Co.*, 224 F.3d 1328, 1330 (Fed. Cir. 2000); *Abbott Labs. v. Teva Pharms. USA, Inc.*, 2005 WL 1026746, at *5 (D. Del. Apr. 22, 2005) ("the specification clearly states, '[i]n the context of this invention, the expression "inert hydrosoluble carrier" means . . . .' I cannot imagine a clearer way of expressing the intention that a particular term be given a particular meaning.") (a copy of *Abbott Labs. v. Teva Pharms. USA, Inc.* is attached in Ex. 10). Thus, when aniline is used as the solvent, the patentees defined a "controlled amount" of protic material to mean that the content of water can be no greater than about 4% by volume. There was no equivocation on this point.

The ALJ correctly recognized that Respondents did *not* argue that aniline must be the solvent or that water must be the protic material; only that *when* aniline is the solvent, water must not exceed about 4%.[7] (ID at 44, 47.) The ALJ also noted that, in accordance with the

[7] In one instance, however the ALJ mistakenly stated that Respondents urged a construction under which "the protic material should be limited to water when aniline is the solvent." (ID at 44.) Respondents never took such a position.

governing principles of claim construction, the specification of a patent acts as a dictionary "when it expressly defines terms used in the claims." (ID at 40, citing *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).) However, he gave little weight to the well accepted law that a patentee can act as his own lexicographer to provide such an express definition for a claim term. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (*en banc*). He also disregarded the law that where it is clear that the specification reveals an intentional disclaimer or disavowal of claim scope, the inventor's intent as expressed in the specification is dispositive. *Id.* The ALJ committed legal error by disregarding the patentees' express definition that a "controlled amount" of protic material means that water cannot exceed "about 4%" when aniline is the solvent. (ID at 91-93.) The 4% water limitation when aniline is the solvent was not an idle remark made by the patentees in mere passing; it is an express definition. The limitation is expressly mentioned four times in the specification. (Ex. 12, col. 4, lines 31-60; Ex. 2, col. 5, lines 27-55.)

Flexsys, Respondents, the ITC staff, and the ALJ all agreed that the claim term "controlled amount" of protic material had no plain and ordinary meaning to one skilled in the art. (ID at 48.) In other words, the patentees were their own lexicographers. Thus, the explicit definition for that term provided by the patentees in the specification is paramount and dispositive. *Phillips*, 415 F.3d at 1316. The ALJ legally erred by ignoring the express definition – the express about 4% water limitation when aniline is the solvent.[8]

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[8] The ALJ may have been confused as to whether it was necessary to address a "global" claim construction, *i.e.*, one that construed the claims with respect to all potential solvent systems, or only with respect to aniline – the solvent used in Sinorgchem's accused process. (ID at 45-48.) The ALJ stated that Respondents urged the Judge "to construe controlled amount of protic material only with reference to the accused process." (ID at 45.) To the extent this statement means that the accused process is relevant to frame the issues in the Investigation, it is correct.

[*Footnote continued on next page*]

The present case is strikingly similar to the Federal Circuit's decision in *Cultor Corp. v. A.E. Staley Mfg. Co.*, 224 F.3d 1328 (Fed. Cir. 2000). In that case, the patents claimed a process for making a polydextrose composition. *Id.* at 1330. The pertinent claims said nothing about the use of citric acid as the catalyst in the claimed process, but the Court construed those claims to require the presence of citric acid, based on the patentees' express definition. That definition read, much like the definition in quotation marks in the present case, as follows:

> As used herein, the expression *"water-soluble polydextrose"* (also known as polyglucose or poly-D-glucose) specifically refers to the water-soluble polydextrose prepared by melting and heating dextrose (also known as glucose or D-glucose), preferably with about 5-15% by weight of sorbitol present, *in the presence of a catalytic amount* (about 0.5 to 23.0 mol%) of *citric acid.*

Id. Based on this express definition, the claims were limited to processes using citric acid as the catalyst. *Id.* at 1331. The same reasoning should apply to define the explicit term "controlled amount" in the present case. The ID does not even mention – much less distinguish – the decision in *Cultor*, which was highlighted by Respondents before the ALJ.

In addition to *Cultor*, the Federal Circuit has repeatedly found that patentees are bound by a clear definition of a claim term set forth in the specification. In *Durel*, 256 F.3d at 134, the Federal Circuit found an express definition set forth in the specification binding, even if that definition were to exclude preferred embodiments inherently disclosed in the examples. Similarly, in *AstraZeneca AB v. Mut. Pharm. Co.*, 384 F.3d 1333 (Fed. Cir. 2004), the Federal

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[*Footnote continued from previous page*]
Indeed, the ALJ correctly acknowledged that "it may be impossible sometimes to frame a claim construction issue without reference to the accused infringement." (ID at 47.) *See also,* Robert L. Harmon, *Patents and the Federal Circuit*, § 6.7(c), and n. 297 (7th Ed. (2005). Respondents never urged that the Sinorgchem process in and of itself is relevant to the meaning of the claims.

Circuit rejected a patentees' argument that express statements describing solubilizers suitable in the claimed invention referred only to preferred embodiments; the court refused to construe the claims to be broader than the patentee's express definition. *Id.* at 1340 ("The inventor's lexicography alone works as an implicit disavowal."); *see also Multiform Desiccants, Inc. v. Medzam, Ltd.*, 133 F.3d 1473, 1478 (Fed. Cir. 1998) ("When the specification explains and defines a term used in the claims, without ambiguity or incompleteness, there is no need to search further for the meaning of the term."); *Abbott Labs. v. Novopharm Ltd.*, 323 F.3d 1324, 1330 (Fed. Cir. 2003) (limiting the claim term "co-micronization" to the explicit definition in the specification). The ALJ ignored all of this highly relevant and controlling precedent.

Moreover, the only *express* teachings in the examples regarding the effect of water emphasizes the deleterious effect of exceeding 4% water when aniline is the solvent. Both the '063 and '111 patents contain Example 3, an example explicitly designed to illustrate the importance of controlling the amount of water as the protic material. The ALJ correctly found that Example 3 discloses an experiment in which "all reaction variables were held constant, except for the amount of protic material (water or methanol)." (ID at 64.) It is clear that the data in Example 3 shows that yields of 4-ADPA intermediates plummeted as water levels rose above 4%, when aniline is the solvent. (ID at 65, Table 2; *see also* Exhibit 11, corresponding to RDX 1, depicting the results reported in Example 3). Example 8 is similar to Example 3, albeit with DMSO as the solvent.[9]

[9] The ALJ incorrectly ignored the express definition and instead focused on Example 10. However, Example 10 is designed to show an aerobic reaction condition and does not expressly disclose the amount of water.

Also figuring in the ALJ's decision was the fact that "there are a number of reaction variables" for producing 4-ADPA intermediates (ID at 80) and his conclusion that a person skilled in the art would understand "the importance of certain reaction conditions for producing 4-ADPA intermediates." (ID at 81.) The ALJ remarked that one skilled in the art "would understand that when conditions are applied to the reaction in issue, the *amount of protic material tolerated will vary.*" (ID at 91.) Even assuming that it is scientifically possible to obtain acceptable results using water in excess of 4%, when the solvent is aniline, that fact is not a legally justifiable reason for ignoring the patentees' express definition for "controlled amount" of protic material. Respondents have found no case in which the Federal Circuit has disregarded a patentee's express definition of a claim term in favor of what might be scientifically feasible. In fact, the Federal Circuit has held that the opposite is true. *See Watts v. XL Systems, Inc.*, 232 F.3d 877 (Fed. Cir. 2000). In *Watts*, the Court stated:

> Watts [the patentee] argued that one of ordinary skill in the art would be aware of myriad ways to effect a scaling connection, such as by using o-rings. *While this may be true, it does not overcome the fact that the specification specifies that the invention uses misaligned taper angles.*

Id at 883. Thus, the ALJ erred, as a matter of law, by relying on what one skilled in the art might be able to achieve, rather than the clear and unambiguous 4% water limitation defined in the patent specification.

Additional sources of the ALJ's legal error on claim construction in the ID are further discussed below.

First, the ALJ incorrectly discounted the "about 4% water" limitation, when aniline is the solvent, because the relevant portions of the patent specifications at issue (which the ALJ referred to as the "PARAGRAPH" (ID at 59-60)) uses the qualifiers "generally," "about," "*e.g.*."

(ID at 82, 91.) A careful read of the patent specification indicates that those modifiers merely acknowledge a point not in dispute – that solvents other than aniline may be used. However, when aniline *is* the solvent, the patent states repeatedly and unequivocally, that the amount of water should not exceed "about 4%." Overlooked by the ALJ is that the express definition for "controlled amount" of protic material includes the following statement:

> When aniline is utilized as a solvent with the same base [TMAH], the upper limit is 4% H2O based on the volume of the reaction mixture.

Ex. 1, '063 patent, col. 4, lines 58-60; Ex. 2, '111 patent, col. 5, lines 52-55. There is no qualifying language here: no "*e.g.*," no "generally," nothing to indicate that the 4% limitation is optional or limited only to specific conditions. Similarly, for much the same reasons, the ALJ's conclusions that the 4% water limitation when aniline is the solvent is limited to ambient conditions is legally incorrect. (ID at 91.) There is simply no basis for such a constrained reading of that portion of the patent specification. Indeed, the relevant portion of the '063 patent – col. 4, lines 32-60 – says absolutely nothing about ambient conditions (or any pressure, temperature, or oxygen level for that matter). Thus, the patentees' "about 4%" water definition when aniline is the solvent is not limited only to ambient conditions. The ALJ's contrary conclusion is based on the testimony of Flexsys' expert, which testimony cannot be used, as a matter of law, to alter the express definition of a claim term. *Phillips*, 415 F.3d at 1318.

Second, the ALJ seems to have incorrectly put weight on the conclusion that "the patentees did not *intentionally* define controlled amount of protic material to exclude various examples in the patent. (ID at 89.) It is well-established that the patentees' subjective intent is not a factor in arriving at a claim construction. *Phillips*, 415 F.3d at 1317. What governs is the "inventor's lexicography." *Id.*

Third, the ALJ incorrectly placed weight on the fact that there is no mention of a numerical maximum amount of protic material in the "Abstract," "Field of Invention," "Related Art," and "Summary of the Invention" sections, or in the introductory portions of the "Detailed Description of the Invention" in the patents. (ID at 53-57.) This observation misses the point. Later on, in the "Detailed Description of the Invention," the patents expressly define "controlled amount" of protic material to mean no more than about 4% water, when aniline is the solvent. An express definition is an express definition, regardless of where it appears in a patent. The ALJ cites to no case law – nor is there any – requiring an express definition to appear in each section of a patent, in order to be given force.

Finally, the ALJ described at length both independent and dependent claims that are not asserted in this investigation. (ID at 50-53.) Although not explicit, the ALJ's decision may have been based, in part, on the doctrine of claim differentiation. However, claim differentiation arguments can only lead, in some limited circumstances, to presumptions regarding claim construction. When, as here, a patentee defines a claim term, claim differentiation arguments cannot change that meaning. *O.I. Corp. v. Tekmar Co. Inc.*, 115 F.3d 1576, 1582 (Fed. Cir. 1997) ("Although the doctrine of claim differentiation may at times be controlling, construction of claims is not based solely upon the language of other claims; *the doctrine cannot alter a definition that is otherwise clear* from the claim language, description, and prosecution history."). In a word, a clear definition "trumps" the doctrine of claim differentiation. Thus, the express definition for "controlled amount" of protic material cannot be altered for that reason.

B. All Embodiments In A Patent Need Not Be Covered By The Claims

The ALJ appears to have believed that a claim construction must necessarily cover all of the embodiments in a patent. (ID at 79, 89-90.) On the contrary, the law is clear that not

everything disclosed in a patent specification must be covered by the claims. *Novo Nordisk v. Genentech, Inc.*, 77 F.3d 1364, 1369 (Fed. Cir. 1996) ("While claims are to be interpreted in light of the specification, all that appears in the specification is not necessarily within the scope of the claims and thus entitled to protection.").[10] Rather, where, as here, there is a clear definition of a critical claim term, the law requires that the patentees' definition is binding. *Durel*, 256 F.3d at 1304 (court relied on express definition even though it might not cover an embodiment); *c.f. Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1326 (Fed. Cir. 2001) (certain disclosed embodiments describing user initiated communications not included in claim construction based on teachings in the specification).

1. Example 10 Cannot Change The Express Definition

The ALJ's claim construction was influenced by the erroneous belief that the claims must cover original Example 10 in the patents. (ID at 89.) There is no dispute that Example 10 does not expressly recite the amount of water in the reaction. (ID at 69-70.) The ALJ found, however, that one skilled in the art could, after making certain assumptions, calculate an approximate water content of 9-10% for the reaction of Example 10. (ID at 86.) Even assuming that Example 10 represents an inherent teaching of a reaction using aniline as a solvent and with water in excess of 4%, the patentees' express definition of the claim language, with the 4% water limitation, must control, as a matter of law. The ALJ cited to no case – nor is there any – where an express definition of a claim term was disregarded in favor of a more expansive, contrary

[10] The ALJ relied on *Vitronics Corp.*, 90 F.3d at 1583, for the position that construing a claim to exclude a preferred embodiment is "rarely, if ever, correct and would require highly persuasive evidentiary support." (ID at 89.) However, in *Vitronics*, unlike the present case, there was only one embodiment described in the patent. In addition, the express definition for "controlled amount of protic material" in the present case certainly qualifies as "highly persuasive" evidence of the proper meaning of the claims.

definition based on *inherent* teachings of an example. When confronted with similar facts, the Federal Circuit has stated that, as between an explicit definition and an inherent disclosure in an example, the explicit definition governs claim construction, even where that definition would exclude a preferred embodiment. *Durel*, 256 F.3d at 1304.

2. The New Matter In The Continuation-In-Part Application For The '111 Patent Cannot Change The Express Definition In The '063 Patent

The ALJ's analysis also demonstrates a reluctance to adopt a claim construction that would exclude Examples 13 and 15 and claim 29,[11] all found *for the first time* in the continuation-in-part '111 patent. (ID at 89-90.) However, as discussed below, these examples and claim 29 cannot undo the express 4% water limitation when aniline is the solvent.

To begin, all of the parties and the ALJ agree that the claim term "controlled amount" of protic material should be construed the same way in the related '063 and '111 patents. (ID at 44, 79, n. 24.) Thus, the meaning that term had in the '063 patent is binding on the later-filed '111 patent. Further, nothing in the new examples and claim first appearing in the continuation-in-part '111 patent should serve to retroactively *broaden* the meaning of the claims in the earlier '063 patent.

The ALJ cited *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1334 (Fed. Cir. 2003) for the proposition that related applications can be looked to for claim interpretation. (ID at 79 n.24.) However, in *Omega*, a *narrowing* disavowal in a parent application was deemed binding

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[11] Claim 29 of the '111 patent is directed to the amount of water at the *beginning* of the coupling reaction and is silent as to the amount of water during the reaction. New example 15, on which claim 29 is based, describes continuous distillation of water throughout the reaction. Thus, claim 29 is not inconsistent with the about 4% claim limitation on water content during the reaction.

on a *later* continuation-in-part application. *Omega*, 334 F.3d at 1333-34. Here, at Flexsys' urging, the ALJ impermissibly used new Examples 13 and 15 and claim 29 in the later filed '111 continuation-in-part patent to reach a *broader* claim construction that was then made retroactively applicable to the earlier '063 patent. The *Omega* case does not support such an incongruous result. Indeed, correctly read, *Omega* supports construing the claim term "controlled amount of protic material" in the '063 and '111 patents without regard to new Examples 13 and 15 and new claim 29, which appear only in the later '111 patent. *Omega*, 334 F.3d at 1333-34; *see also Wang Labs., Inc. v. Am. Online, Inc.*, 197 F.3d 1377, 1383-84 (Fed. Cir. 1999) (description of prior art in Information Disclosure Statement filed in parent application limited claim in later filed continuation-in-part application).

In sum, the ALJ erred, as a matter of law, in arriving at a claim construction based on either Example 10 of the '063 patent or Examples 13 and 15 and claim 29 of the '111 patent, rather than the express definition for "controlled amount" of protic material.

C. The ALJ's Claim Construction Is Contrary To The Public Notice Function Of Patent Claims

The claim construction adopted in the ID is contrary to the public notice function of claims. Based on the patentees' express definition, the claim term "controlled amount" of protic material means that when aniline is the solvent, the amount of water must be kept at about 4% or less. Respondents and the public at large have a right to rely on such a definition that sets forth the scope of the claimed subject matter. *See PCS Computer Prods., Inc. v. Foxconn Int'l, Inc.*, 355 F.3d 1353, 1359 (Fed. Cir. 2004) ("one of ordinary skill in the art should be able to read a patent, to discern which matter is disclosed and discussed in the written description, and to recognize which matter has been claimed."); *Exxon Chem. Patents, Inc. v. Lubrizol Corp.*, 64

F.3d 1553, 1563 (Fed. Cir. 1995, J. Plager, concurring) ("The public generally, and in particular, the patentee's competitors, are entitled to clear and specific notice of what the inventor claims as his invention."). Indeed, Sinorgchem's own patents, filed before this Investigation commenced, distinguished the Flexsys patents on the basis of the 4% water limitation, when aniline is the solvent. (Ex. 12 corresponding to RX-707; Ex. 4, Tr. 1222:16-23, 1227:2-5, 1229:2-1230:1.) Similarly, Dr. Fu, Sinorgchem's expert, explained that anyone skilled in the art, after reading the entire patents, would come away with the clear conclusion that the patentees had decided, based on experimental data, that 4% water is the upper limit when aniline is the solvent and TMAH is the base. (Ex. 4, Tr: 1462; 1-21.) Nothing in the patents or at trial supports a contrary interpretation of the public record.

The ALJ's approach to claim construction does a real disservice to the all-important public notice function of the claims in patents. In *Markman*, 52 F.3d at 978, the Federal Circuit stressed the need for the public to have notice of the scope of patent claims. The Supreme Court agreed with that sentiment, cautioning against a "zone of uncertainty" in patent claims that would serve to "discourage invention" by others in the field. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 390 (1996).

Unless the erroneous claim construction proffered by Flexsys and accepted in the ID is corrected, the public would be precluded from relying on the patentees' express definition of the claim language, based on the data in Example 3 in the specification directly confirming that express definition. Instead, under the erroneous claim construction in the ID, the public would be required to hire experts to perform various calculations (using many underlying, undisclosed assumptions), relating to all of the examples, and then guess whether the amount of protic material falls within the minimum and maximum amounts required for a "controlled amount."

Finally, as will be discussed further, the ALJ's claim construction is also flawed because it results in the asserted claims being indefinite in violation of 35 U.S.C. § 112, ¶ 2. Under the ID, contrary to the express "about 4% water" definition when aniline is the solvent, the claims could cover aniline systems with water reaching *any amount*, so long as the reaction subjectively works and the subjectively "desired" selectivity is obtained. Invalidity for indefiniteness (discussed further in Section V, *infra*) is yet another reason why the ALJ's claim construction cannot stand.

V. THE ALJ ERRED IN DETERMINING THAT THE ASSERTED CLAIMS OF THE '063 AND '111 PATENTS ARE NOT INDEFINITE

The ALJ accepted the Flexsys construction of the phrase "controlled amount" of protic material (also referred to herein as "the claim term") to mean:

> the amount of protic material (which is not limited to water) should be controlled between (1) *an upper limit* of protic material which is the amount of protic material beyond which the *reaction* between nitrobenzene and aniline (or substituted aniline) *is inhibited* and (2) *a lower limit* of protic material which is the amount of protic material below which the *desired selectivity* for 4-ADPA intermediates is not maintained.

(ID at 78-79.) In support of that claim construction, Flexsys made it clear that the amount of protic material "must be controlled between a maximum and a minimum in order to obtain *high conversion [yield] of nitrobenzene* and to *maintain selectivity of the* desired 4-ADPA *intermediates*. (Ex. 13, corresponding to Flexsys' Post-hearing Brief, at 3.) Exceeding the maximum inhibits the reaction of nitrobenzene "to an extent where the reaction is no longer significant," (Ex. 1, col. 4, lines 36-37; Ex. 2, col. 5, lines 32-34), *i.e.,* a "low yield" is obtained (Ex. 1, col. 2, lines 1-2; Ex. 2, col. 2, lines 7-9). Exceeding the minimum maintains the desired

selectivity and results in a reaction mixture "rich in 4-ADPA intermediates." (Ex. 1, col. 2, lines 24-26; Ex. 2, col. 2, lines 31-34.)

The ALJ concluded that a person of ordinary skill in the art would not find the claim term indefinite as construed above. (ID at 119.) To comport with the definiteness requirement of 35 U.S.C. § 112, the amount of inhibition of the reaction defining the "upper limit" of the amount of protic material and the degree of "desired selectivity" for the desired intermediate products defining the "lower limit" of protic material must be reasonably clear and definite to one skilled in the art. To be reasonably clear and definite, "[s]ome objective standard must be provided in order to allow the public to determine the scope of the claimed invention." *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1350 (Fed. Cir. 2005). Neither the ALJ nor Flexsys (including Flexsys' inventors and experts) provided any objective standard for a person of ordinary skill to determine the *amount* of inhibition or the *degree* of desired selectivity encompassed by the claimed term. Rather, the overwhelming testimony is that the amount of inhibition and the degree of desired selectivity is entirely subjective. The ALJ's conclusion on indefiniteness, therefore, is legally erroneous.

The ALJ concluded that no maximum or minimum limits on the amount of protic material is set forth anywhere in the specification of the patents-in-suit. (ID at 49, 54, 57-58.) The ALJ further concluded "that a quantitative definition for the term 'controlled amount of protic material' would not be indicated to a person of ordinary skill in the art for interpreting 'controlled amount of protic material.'" (ID at 79, n.23.) In addition, the ID concluded that the claim term "is not generally used in chemistry and has no clear meaning to readers." (ID at 48.) Despite the fact that the ALJ was unable to find any maximum or minimum limits in the '063 or '111 patents or any evidence of a quantitative definition at trial, and that the inventors and

experts all testified that it was a subjective determination, the ID incorrectly concludes "that the disclosures of the '063 and '111 patents, supplemented by the prosecution history, do provide an *objective* definition for the claimed term . . . ." (ID at 118-19.)

A. The Patents Do Not Describe The Upper And Lower Limits Of The Protic Material

The ALJ incorrectly held that:

> the [patent] specifications provide a number of examples through controlled experiments that would permit said person [one skilled in the art] to determine the specific upper and lower limits of protic material for a specific set of reaction conditions and that the prosecution history even provides calculations. (ID at 116.)

First, the ALJ does not point to a single example that would permit one to determine both the upper and lower limits of protic material required by the claims. Indeed, although the ALJ recounts the teachings of *all* of the various examples in the patents, in *none* is there a teaching – express or implied – of both the upper and lower limits for protic material or any *objective* criteria for determining such limits. (ID at 62-72.) To be sure, the examples might *enable* one to practice the claimed subject matter. However, the enablement and definiteness requirements of 35 U.S.C. § 112 are separate and distinct. *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993); *Personalized Media Commc'ns, LLC v. U.S. Int'l Trade Comm'n,* 161 F.3d 696, 707 (Fed. Cir. 1998) ("citation of evidence bearing solely on § 112, ¶ 1 infirmities does not aid the Commission in supporting the ALJ's indefiniteness holding under § 112, ¶ 2 . . . ."). As stated by the Federal Circuit, "[t]he invention's operability may say nothing about a skilled artisan's understanding of the bounds of the claim." *Miles Labs.*, 997 F.2d at 875. Thus, the disclosure in the examples does not save the claims from invalidity due to indefiniteness.

Second, although the prosecution history provides sample calculations of selectivity and water content (ID at 73, 74, 76), these calculations provide no objective basis for determining both the upper and lower limits for protic material in the claimed invention. Calculating a yield, selectivity, or water content "for a set of reaction conditions" (ID at 116) says nothing about how to objectively determine the upper and lower limits for protic material. As with the examples, the prosecution history provides no roadmap, no guideposts, and no explanation for the public to ascertain the metes and bounds of the claimed invention as construed by the ALJ. Thus, the underpinnings of the ALJ's decision on the indefiniteness issue are incorrect.

In sum, the asserted claims are indefinite because there is no "objective way" to determine whether one is practicing the claimed invention. *Datamize*, 417 F.3d at 1352. The failure on the part of the inventors and Complainant's experts to set forth any objective basis for determining the scope of the claims, discussed below, further shows that the claims are invalid as indefinite.

B. Neither Complainant's Experts Nor The Inventors Provided Any Objective Standard To Determine The Amount of Inhibition Or The Degree Of "Desired Selectivity" Encompassed By The Claimed Term

Not only is the ALJ's finding of an "objective definition" of the claim term unsupported, it is directly contradicted by every inventor that testified at trial (Drs. Stern, Bashkin, and Rains), as well as Flexsys' chemistry expert, Dr. Crich. Flexsys' inventors and expert repeatedly asserted that the amount of protic material must be sufficient to provide high conversion of nitrobenzene, *i.e.*, high yield, and maintain selectivity to produce a "rich" amount of 4-ADPA intermediates. (Ex. 4, Tr. 444:6-20; 788:20-789:21; 1007:20-1009:1.) But these same witnesses repeatedly failed to provide a single objective criteria for determining the amount of conversion or degree of richness encompassed by the claimed term. *Id.* Moreover, the witnesses candidly

set forth lists of subjective factors affecting the scope of the claim term. To emphasize the subjective nature of the ALJ's erroneous claim construction, a collection of testimony from Drs. Crich, Stern, Bashkin, and Rains is contained in Exhibit 4, attached hereto.

When asked what the minimum and maximum amounts of protic material were for the given set of reactive conditions using DMSO as the solvent in Example 8, Dr. Bashkin could not answer. Example 8 was designed to illustrate the effect the amount of protic material, *i.e.*, the control of protic material, has on nitrobenzene conversion, yield and selectivity of 4-ADPA intermediates. (Ex. 1, col. 11, lines 10-13; Ex. 2, col. 12, lines 27-29.)

> Q. Can you tell me from the data that's reported in example 8 what the minimum and maximum amount of protic material that should be used to obtain acceptable results in terms of yield and selectivity?
> A. . . . So we've had considerable discussion from both sides that what's acceptable depends on the local situation or the conditions under which one skilled in the art is interested in practicing this invention. So the answer is that this is one of a set of examples designed to explain and show and teach how one skilled in the art can determine optimal examples for his own personal or company situation, and *I wouldn't presume to say the best results for someone whose situation I'm not aware of.*
> Judge Luckern: *So he can't answer the question.*

(Ex. 4, Tr. 2150:1-23.) Thus, it is undisputed that, even for a very specific set of reaction conditions, Dr. Bashkin, one of the inventors, could not identify the minimum and maximum amounts of protic material that were within the claimed term.[12]

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[12] Dr. Bashkin's inability to answer is not surprising given the confusing and inconsistent data in Example 8. A cursory review of the data for % water, conversion, and yield in Example 8 demonstrates that the optimum amount of protic material approaches zero. Specifically, as the water in Example 8 decreases, conversion and yield steadily increase. The highest reported yield and conversion are obtained with the least amount of water. As Dr. Beckman testified, selectivity "bounces around." (Ex. 4, Tr. 2050:6-23.) In contrast, when the water is increased conversion and yield steadily decrease. Thus, based on this data, one of ordinary skill in the art

[*Footnote continued on next page*]

When Dr. Bashkin was asked more generally about the amount of protic material that satisfied the definition of the term "rich" in 4-ADPA intermediates, as used in the patents, his response was equally deficient. He said it "depends on the circumstances." He elaborated on the various circumstances:

> Q. What kind of circumstances?
> A. It depends on solvent, it depends on the base, it depends on the temperature, it depends on whether you are running a continuous or a batch process. It depends on what pressure you are running it at. *It depends on what country you are in and what the raw materials costs and energy costs are.* It depends on what kind of purification processes are cost-effective for you or not, et cetera, et cetera. So it is an economic and business decision, as much as a chemistry decision, or even more so. And that's why it is left to – *it has to be left to the individual practitioner, if they feel the chemistry is effective enough to practice, and practice it, then they have made the decision that it is rich enough for their purposes.*
> Q. And that determination depends upon at least the factors that you just enumerated, correct?
> A. Well, those are example factors.

(Ex. 4, Tr. 400:17-401:21.) Again, Dr. Bashkin provided no objective basis for determining the metes and bounds of a "controlled amount" of protic material.

Dr. Rains, a named inventor on the '111 patent and an expert for Flexsys, testified similarly. The term "controlled amount," according to Dr. Rains, implied a reaction product that is "rich" in 4-ADPA intermediates, indicating a "high yield or high selectivity." (Ex. 4, Tr. 788:20-789:21.) When explicitly asked about the amount of richness covered by the patent claims, Dr. Rains responded that it was "implicit" and "subjective:"

[*Footnote continued from previous page*]
would conclude that the highest yield and conversion are obtained with minimal or even zero amounts of water, *i.e.,* less than 2%. However, the patents do not provide data where water is less than 2%. *Id.* Attached, as Exhibit 14, is a chart summarizing the data in Example 8.

Q. And nowhere in these claims, claim 30, claim 61 or claim 1 is there any limitation on the yield of product that's stated in those claims, is there?
A. *It is implied if you want to achieve a product that is rich in the 4-A[DPA] intermediates, which would indicate a high yield or high selectivity*, that's implied in the discussion of controlled amount, the presence of a controlled amount of protic material, which discusses that particular issue.
Q. Let's look at claim 30. You are talking about, there is language, the presence of a controlled amount of protic material, that's in step B, correct?
A. That is correct.
Q. And you are saying that that is an implied yield requirement?
A. Discussion in the text talks about controlling the amount of material between a minimum and a maximum to maintain selectivity and to, in the upper limit, to keep the reaction from going, from stopping. *So you want to operate in that range and you want to operate in a range to maintain the selectivity, which is a high selectivity, so that it is rich in 4-A[DPA] intermediates.*

(Ex. 4, Tr. 788:20-789:21; *see also* Tr. 789:22-791.5.) Rains clearly conceded that the amounts of yield or richness covered by the patent claims was entirely subjective:

Q. What is the amount of yield that should be, in your view, read into this claim?
A. *It is a subjective number. You can't put an absolute number on it* because it depends on a number of circumstances. And what might be acceptable for one company may be too low for another company, so it really depends on circumstances.
Q. Can you give me any more definite statement than that as to what the yield would be of 4-ADPA that would be related to the controlled amount of protic material?
A. Not at this time, no.

* * *

Q. What is the lowest percentage of yield or selectivity that in your view would fall within the patent claims as you are defining?
A. *I can't put a number on it. Again, it is a subjective number.*

(Ex. 4, Tr. 789:22-791.5; *see also* Tr. 793:24-794.9.) Rains further testified that as long as the process achieved "practical results," it would be understood as using a "controlled amount" of

protic material. (Ex. 4, Tr. 788:20-793:23). Rains, however, could not identify what yield would represent "practical results" and that the definition besides being subjective was relative, depending on many factors, such as location and labor costs:

> Q. But you can't say where that point is?
> A. No, because what's practical someplace may not be practical somewhere else. If you have a very low labor cost, you can afford to have a lower selectivity because you can make it up on labor cost. I mean, as an example. So there is no definitive number on what is impractical.
> Q. *That's because rich is a relative term, right, sir?*
> A. *Yes, it is.*

(Ex. 4, Tr. 793:24-794:9.) Dr. Rains further admitted that Flexsys' conversion and richness limitations; *i.e.*, the maximum and minimum amounts of protic material, depend upon "a number of circumstances" such as "labor costs." (Ex. 4, Tr. 789:22-791:5.) As noted, Dr. Rains ultimately admitted that Flexsys' proposed claim construction, which was adopted by the ALJ, is *purely subjective*. (Ex. 4, Tr. 144:6-20; 790:3-791:5.)

At the hearing, inventor Dr. Stern also acknowledged there is no objective standard that would allow the public to determine the scope of the claim term. In fact, Dr. Stern was not even able to provide a coherent answer as to whether the experiments set forth in Example 3 of the '063 patent were conducted with a "controlled amount" of protic material. (Ex. 4, Tr. 614:14-618:7.) According to Dr. Stern, although Example 3 demonstrates a relationship between the amount of controlled material and yield and selectivity of the reaction, he was unable to provide a clear answer as to which reactions in Example 3 produced sufficient yield and selectivity to fall within the "controlled amount" claim limitation.

The testimony of Flexsys' retained expert, Dr. Crich, was no different. Like Drs. Rains, Bashkin and Stern, Dr. Crich could not identify any objective criteria for determining the level of yield or richness required by the Flexsys' construction of the term "controlled amount":

> Q. In the context of the '063 and '111 patents, what is an optimized yield?
> A. *An optimized yield is a good yield.* If you were to look at the yield of the invention, you would see that the amount of protic material is controlled to provide a mixture rich in the 4-ADPA intermediates.
> Q. And what's a good yield in terms of numerical values?
> A. *It all depends what you're seeking to do.*

(Ex. 4, Tr. 1007:20-1008:5.)

As the above testimony overwhelmingly indicates, if the inventors and experts cannot determine whether specific examples in the patents produce enough yield and selectivity to fall within the scope of the claim term, the public certainly cannot determine what process would meet this subjective limitation.

C. The *Datamize* Decision Is Controlling

The ALJ found that *Datamize* was distinguishable on its facts. (ID at 118.) As described in the ID, the court in *Datamize* concluded that appellant had offered no objective definition identifying a standard for determining when an interface screen is "aesthetically pleasing." *Datamize*, 417 F.3d at 1350-51. The ID, however, fails to explain any meaningful difference between the lack of objective standards in *Datamize* for the phrase "aesthetically pleasing" and the lack of objective standards in the Flexsys' patents for a "controlled amount" of protic material.

The similarities between the claim term here and in *Datamize* are striking. In *Datamize*, the patentee argued that the claim term "aesthetically pleasing," applied to the process of

defining a "desired result" and not the actual process itself. *Datamize*, 417 F.3d at 1349. The Federal Circuit held that the desirability of the "aesthetically pleasing" result does not alter the inherent subjectivity of the term. *Datamize*, 417 F.3d at 1349-50. Similarly, the ALJ here concluded that the term "controlled amount" of protic material requires obtaining a "desired selectivity." As in *Datamize*, however, the desirability of obtaining that result does not alter that "desired" selectivity is inherently subjective.

In *Datamize*, the patentee cited statements within the specification describing advantages over the prior art and examples of aesthetic features. The Federal Circuit stated:

> In general, neither of these statements nor any others in the written description set forth an objective way to determine whether an interface screen is "aesthetically pleasing." The description of the advantages of the invention indicates that there are "good standards of aesthetic," which of course implies that there are also standards of aesthetics that are "not good." The inventor does not attempt to explain what distinguishes the two, except to say that experts, specialists, and academics may have views that are influential in determining what aesthetic standards are good.

Datamize, 417 F.3d at 1352. Similarly, the ALJ here concluded that the "Background of the Invention" and the "Summary of the Invention" sections of the Flexsys patents inform the public that the amount of protic material (*e.g.*, water) is controlled to produce a mixture that is "*rich* in 4-ADPA intermediates." (ID at 53-56) (emphasis in original). This, of course, implies that there are also amounts of protic material that produce mixtures that are not "rich." The specifications of the '063 and '111 patents do not attempt to define "rich." Rather, the ALJ simply concludes that "a person 'experienced in the field' of the invention in issue, and not merely a person with no chemical background, would understood [*sic*] the meaning of 'controlled amount of protic material' in view of the claims and the specifications of the '063 and '111 patents and the prosecution history." (ID at 119.) As in *Datamize*, however, these statements fail to set forth an

objective way to determine whether an amount of protic material produces a mixture that is "rich."

In *Datamize*, the patentees presented experts attempting to "identify parameters that one skilled in the art might reference when attempting to determine whether an interface screen is 'aesthetically pleasing.'" *Datamize*, 417 F.3d at 1354. The Federal Circuit rejected the experts' declarations, noting that "[t]he inability of the expert to use the parameters he himself identified to determine whether an interface screen is 'aesthetically pleasing' militates against the reasonableness of those parameters as delineating the metes and bounds of the claim." *Datamize*, 417 F.3d at 1354. Similarly, as discussed above, Flexsys presented three inventors, Drs. Stern, Bashkin, and Rains, as well as a chemistry expert, Dr. Crich, all of whom attempted to identify parameters that affect the degree of desired richness and yield. Therefore, as in *Datamize*, the inability of the inventors and experts to determine which sets of reaction conditions encompassed by the claims demonstrates the subjectivity of the metes and bounds of the claim term.

D. The *Exxon* Decision Supports A Finding Of Indefiniteness

The ALJ found that *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371 (Fed. Cir. 2001) supports a holding that the claimed term is not indefinite. The ID, however, fails to note key differences between the specifications at issue in *Exxon* and the specification of the '063 and '111 patents.

In *Exxon Research*, the specification provided an objective standard for the claim term at issue, "substantially increased," by setting forth a numeric definition of "at least about 30%" and was thus found not indefinite on that basis. *Exxon Research*, 265 F.3d at 1377. Not only do Flexsys' patents fail to provide any numeric limitation on "selectivity," "high yield," or

"richness," all of Flexsys' experts consistently failed to demonstrate the presence of any objective standard at trial. (Ex. 4, Tr. 444:6-20; 1007:20-1009:1.) Thus, according to *Exxon Research*, without an objective standard, such as a numerical limitation, Flexsys' claims are indefinite as "insolubly ambiguous" because one of ordinary skill would not understand "the bounds of the claim." *Exxon Research*, 265 F.3d at 1375. This result is particularly correct when the inventors themselves do not understand "the bounds of the claim." *Id.* Therefore, *Exxon Research* supports a finding of indefiniteness rather than definiteness.

Another basis for the Federal Circuit's refusal to find indefiniteness in *Exxon Research* was the fact that the claim term at issue was – unlike in this case – not a "critical feature" of the invention. Citing the C.C.P.A.'s decision in *In re Jolly*, 172 F.3d 566, 569 (C.C.P.A. 1949), the *Exxon Research* court explained:

> *In re Jolly* concerned an indefiniteness rejection based on similar claim language, "a time sufficient to produce a substantially homogeneous product but insufficient to cause the formation of a substantial proportion of oil-insoluble reaction products." The court there found that since the time of reaction was taught to be critical, the claims must recite a time range for the sulfurization step at issue. While an upper time limit was recited, at least in some claims and in the written description, there was no lower limit recited. For that reason, the court affirmed the examiner's rejection, stating that "[s]o far as the time of reaction is concerned, it seems to us that all that appellant's specification teaches those skilled in the art is to experiment and find out for themselves how much time will be required where different amounts, or proportions, of nitriles and sulfur are used."

Exxon Research, 265 F.3d at 1379.

Like the claim term at issue in *Jolly*, the term "controlled amount" of protic material is clearly a critical feature of Flexsys' patents. The fact that this term is a critical feature is

evidenced by the specification of the patents and the file histories. For example, during prosecution, the patentees distinguished the prior art by stating:

> It was applicants who discovered *the criticality of controlling the amount of protic material* present in the reaction of aniline or substituted aniline derivatives with nitrobenzene. Specifically, neither reference teach controlling the amount of protic material during the reaction by either use of a desiccant or continuous distillation.

(Ex. 3, Preliminary Amendment for the '111 patent at FA030987.) The specification further emphasizes the criticality of the claim term. (Ex. 1, col. 4, lines 30-31 ("Control of the amount of protic material present in the reaction is important") and col. 9, lines 20-21 ("This example illustrates that control of the amount of protic material present in the reaction is important.").)

Moreover, the court in *Jolly* noted that the indefinite character of the claim term at issue was further evidenced by the fact that the meaning of the term *would depend on a large number of variable combinations*. *Jolly*, 172 F.2d at 570. As in *Jolly*, the ALJ requires the public to examine a large number of variable combinations to determine the level of selectivity that falls within the scope of a "controlled amount" of protic material. Even after investigating this large number of variables, one skilled in the art would still have no objective standard to determine whether the level of selectivity is within the scope of a "controlled amount" of protic material."

The asserted claims are invalid due to indefiniteness under 35 U.S.C. § 112.

VI. THE ALJ COMMITTED LEGAL ERROR IN HIS FAILURE TO FIND THE ASSERTED CLAIMS INVALID OVER THE PRIOR ART

It was undisputed that three-step commercial processes for making 6PPD were known for many decades prior to 1990. (Ex.1, col. 5, lines 48-62 and col. 6, lines 3-6; Ex. 3, col. 7, lines 31-42; Ex. 4, Tr. 358:8-359:17; 589-592; 726:16-728:24; 731:1-732:12; 769:2-770:9; 787:18-788:19; 1888:16-1894:11.) In those old processes, step (1) was coupling aniline and PCNB to

form 4-ADPA intermediates; step (2) was reduction thereof to 4-ADPA; step (3) was alkylation of 4-ADPA to 6PPD. The only arguably novel step in the asserted claims, as compared to the known three-step[13] commercial processes, was the use of the chlorine-free reaction of aniline with nitrobenzene, rather than with p-chloronitrobenzene ("PCNB"), in the presence of a base, as steps (a) and (b) of the asserted claims, to form the 4-ADPA intermediates. That chlorine-free first step is what Wohl (Ex. 18) clearly teaches, as explained below.

The ALJ's determination that the asserted claims were not obvious in light of the prior known commercial processes for making 4-ADPA and 6PPD, combined with the 1903 Wohl paper, flowed directly from both his refusal to apply his own findings regarding the problem facing the industry in the late 1980s and the clear motivation to combine Wohl's chemistry with the known commercial processes (ID at 10-11 and 13-14) when he considered Respondents' invalidity argument. In addition, the ALJ's decision was the result of his legally impermissible conclusion that Wohl did not disclose reacting aniline and nitrobenzene in the presence of a base and a "controlled amount" of protic material to make a 4-ADPA intermediate according to the first two steps (a) and (b) of the asserted claims. (ID at 110-12.) That conclusion by the ALJ was directly contrary to the conclusion of all of the tribunals that have looked at that issue. The ITC Staff also agreed that Wohl disclosed steps (a) and (b) of the asserted claims. (Ex. 17, Post-Hearing Brief of the Commission Investigative Staff, at 38.)

In addition, the ALJ's determination of nonobviousness of the asserted claims: (1) was inconsistent with his earlier determination regarding the breadth of the asserted claims and

[13] Steps (a) and (b) of the asserted claims of the '063 and '111 patents correspond to the coupling step (1) of the prior commercial processes.

(2) ignored both the clear teachings of and admissions in the asserted patents and other binding admissions made by Monsanto-Flexsys during prosecution. More specifically, the ALJ committed clear legal error when, after construing the claims broadly as not requiring any particular yield or selectivity for the 4-ADPA intermediates, he determined that combining Wohl with the other well-known commercial steps for making 4-ADPA and 6PPD was not obvious, primarily because Wohl reported relatively low yield and selectivity. The 1903 Wohl paper does, however, describe steps (a) and (b) of the '063 and '111 patents and, in combination with the known prior commercial processes for making 6PPD, makes obvious the asserted claims of the '063 and '111 patents.

The ALJ also (1) improperly relied on proposed but unproven explanations of reaction mechanisms instead of the scientific disclosure of Wohl and (2) improperly accepted and relied on testimony by Flexsys' witnesses that was inconsistent with or contradicted explicit statements made in the patents and the patent prosecution history. Those prior statements were admissions on which the public has a right to rely.

To establish obviousness requires: (1) all the claim limits must be found in the prior art; (2) there must be a motivation to combine the prior art to arrive at the claimed invention; and (3) there must be a reasonable expectation of successfully combining the prior art. *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003). Respondents satisfied these requirements by substantial evidence but the ALJ ignored the evidence and committed legal error.

A. The ALJ Ignored The Substantial Contemporary Evidence Of Motivation To Combine And Is Thus Legally Flawed

The ALJ improperly concluded, without any citation to the record, that the motivation to combine the Wohl aniline-nitrobenzene reaction with the well known second and third commercial process steps for making 4-ADPA and 6PPD was "motivated solely by hindsight." (ID at 113.) The ALJ's use of the convenient legal buzzword "hindsight," however, cannot vitiate the Federal Circuit's consistent statement that a court "may find a motivation to combine prior art references in the nature of the problem to be solved." *Ruiz v. A.B. Chance Co.*, 357 F.3d 1270, 1276 (Fed Cir. 2004). *See also Display Techs., Inc. v. Paul Flum Ideas, Inc.*, 282 F.3d 1340, 1346-47 (Fed. Cir. 2002); *In re Huang*, 100 F.3d 135, 139 n.5 (Fed. Cir. 1996); *Pro-Mold v. Great Lakes Plastics*, 75 F.3d 1568, 1573 (Fed. Cir. 1996).

Respondents' proof of the nature of the problem to be solved was not derived from "hindsight," as the ALJ improperly concluded, but came in the form of contemporaneous (1990 and earlier) evidence, including the patentees' own admission of the problem Monsanto management provided to Dr. Bashkin and other scientists in Monsanto's research department in 1990. The problem was to eliminate chlorine and associated byproducts resulting from use of PCNB in the process of synthesizing 4-ADPA intermediates. According to the legal standard established by the Federal Circuit, the record evidence of this problem, not improper "hindsight analysis," establishes motivation to combine Wohl, a chlorine-free method of producing 4-ADPA intermediates, with the standard reduction and alkylation processes that are steps (c) and (d) of the asserted claims.

The evidence at the hearing showed that by about 1990, but not before, Monsanto had determined that it was no longer feasible to continue using its decades-old process for preparing 4-ADPA and 6PPD because of the generation of large amounts of chlorinated waste. To change

commercial processes was a very expensive undertaking. However, once Monsanto developed the will in 1990 to switch to an environmentally cleaner 4-ADPA process, the way to do so was quickly and obviously apparent.

Conceptually, the '063 and '111 processes differ from the prior art Monsanto commercial process by nothing more than simply using an unchlorinated material, nitrobenzene, in place of the PCNB that had been previously used by Monsanto. In addition, by the use of this conceptual modification, there was no need to tinker with the reduction and alkylation steps already known and used at Monsanto in order to implement the technology of the '063 and '111 patents. However, while this concept provided a solution to Monsanto's chlorinated waste problem, it was neither novel nor patentable in 1990. Long before, Wohl had shown that a 4-ADPA intermediate could be produced by the direct coupling of nitrobenzene and aniline.

The ALJ improperly ignored the substantial evidence Respondents submitted on this point. Worse, the ALJ ignored his own factual findings regarding the state of the industry and the motivation to combine the Wohl aniline-nitrobenzene reaction in the late 1980s. In that regard, the ALJ explained the preexisting method for making 4-ADPA intermediates by reacting aniline with PCNB. (ID at 10-11.) The ALJ also explained the then-recent need, for environmental reasons, to eliminate the production of chloride byproducts, a problem solved by reacting aniline with nitrobenzene instead of chloronitrobenzene. (ID at 13-14). This is exactly the solution offered by Wohl, making it obvious for one skilled in the art to combine Wohl with the well known, existing commercial reduction and alkylation steps to make 4-ADPA and 6PPD. This is the record compelling evidence of motivation to combine that the ALJ improperly ignored his determination on obviousness.

Moreover, Flexsys did not introduce evidence that the new problem facing Monsanto in 1990 – the need to eliminate chloride wastes – was an old one. The totality of the evidence was to the contrary; chloride wastes did not become a motivating factor until 1989 or 1990. (Ex. 4, Tr. 205:4-206:15; 595:18-596:1; 721:18-722:5; 1877:10-1878:22.) Indeed the internal memos that Flexsys relied upon unequivocally show that Monsanto continued to research "improvements" to its chloride waste producing PCNB-based process as late as 1988-1990. (Ex. 4, Tr. 676:1-16; 681:16-683:25; 689:3-690:6; 692:1-19.) Therefore, the ALJ's one sentence conclusion that no one in the eighty-eight years after 1903 "ever considered using the Wohl reaction as a starting point for making 4-ADPA" (ID at 113) is without any legal relevance. The mere fact that Wohl was published eighty-five years before the claimed invention is not by itself of any legal relevance, since the motivation to combine Wohl did not arise until 1990. *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1583 (Fed. Cir. 1996) ("The failure of others was not found to be significant because there was only a brief time period during which manufacturers sought a solution to the problem of increased carbon utilization in aircraft brakes."); *Tex. Instruments, Inc. v. U.S. Int'l Trade Comm'n,* 988 F.2d 1165, 117 (Fed. Cir. 1993) ("Long felt need is analyzed as of the date of an articulated identified position and evidence of efforts to solve that problem.").

The ALJ found that those skilled in the art would not be motivated to use the Wohl process because it primarily taught the production of phenazine and other ortho-substituted products and only a small percent of p-nitrosodiphenylamine by a "side reaction." (ID at 111.) However, this is clearly erroneous in light of undisputed testimony by Dr. Beckman and work in 2000 by Complainant's own chemist, Mr. Triplett. Indeed, those skilled in the art faced with the problem of seeking a replacement for the existing commercial process would not be disturbed or

dissuaded by the fact that Wohl's example produced a low yield or that the reaction was characterized as a "side reaction." Testimony by Dr. Beckman showed that those skilled in the art would recognize that Wohl was not trying to optimize his process, but rather to produce sufficient product in sufficiently pure form that it could be analyzed and identified – and that Wohl succeeded in doing just that. Dr. Beckman's testimony, with which Flexsys' expert Dr. Rains concurred, is that those skilled in the art would readily be able to "tinker" with the conditions of the Wohl example to improve the results. (Ex. 4, Tr. 784:18-785:4; 1967:2-11.) This is confirmed by the work of Flexsys' chemist Mr. Triplett in 2000. (Ex. 4, Tr. 45:14-46:7; 783:11-784:9; 1971:13-1974:4.)[14]

In summary, there can be no doubt on the record that Wohl taught a chlorine-free means of producing a 4-ADPA intermediate. (Ex. 4, Tr. 379-382; 1871; 1966:14-1967:1; 2114:2-2117:4.) This fact is corroborated by objective, unbiased evidence in a text on organic synthesis methods which republished the Wohl aniline-nitrobenzene reaction as the recognized method of making 4-nitrosodiphenylamine (4-NODPA). (Ex. 4, Tr. 1219:6-24; 1923:18-1926:20.) Dr. Stern and others agreed that removal of chlorine from the existing process was "conceptually obvious" and exactly what Wohl did. (Ex. 4, Tr. 222:11-224:7; 595:15-596:17; 733:18-738:18; 1952:20-1955:6.) Given the primary motivation at the time – elimination of chlorine from the existing processes – and that Wohl taught a chlorine-free means of producing a 4-ADPA

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[14] Triplett had a master's degree in chemistry and some industrial experience. On setting to work on the Wohl process, Mr. Triplett ran it successfully. He was able to analyze the resulting product and determined that the Wohl experiment not only produced 3% 4-NODPA but also produced 6% of 4-NDPA, making the actual yield of 4-ADPA intermediates about 9%. Then, in only three experiments, by lowering the temperature, decreasing the amount of base, and adding a second solvent, he increased the yield and selectivity to "high" levels.

intermediate, one skilled in the art would unquestionably have been motivated to use the Wohl reaction in combination with the long-established reduction and alkylation reactions. (Ex. 1, col. 1, lines 23-43; Ex. 4, Tr. 733:18-738:18, 1952:20-1955:6.)

Therefore, the motivation for combining Wohl with the previously known reduction and alkylation steps is clearly found in the nature of the problem to be solved and should not have been subject to the ALJ's unreasoned "hindsight analysis" label.

B. The Wohl 1903 Paper Discloses Every Element Of Steps (a) And (b) Of The Asserted Claims

The ALJ also erred by his improper determination, explained below, that Wohl does not disclose the making of 4-ADPA intermediates according to steps (a) and (b) of the asserted claims. (ID at 113.) The finding of nonobviousness is hence fatally infected with that additional fundamental legal error.

Wohl reports the reaction of aniline and nitrobenzene in the presence of "suitable base" as defined in the patents (sodium hydroxide) to produce a 4-ADPA intermediate, 4-NODPA; Wohl reported the use of aniline in molar excess of nitrobenzene, which the patents describe as the preferred "suitable solvent system" (Ex. 1, col. 3, lines 41-43); Wohl employed a suitable temperature as defined (Ex. 1, col. 4, lines 9-12); and Wohl controlled the amount of protic material by distilling off the water after it was formed during the reaction (Ex. 4, Tr. 2117-2119). Wohl thus discloses every element of steps (a) and (b) of all of the asserted claims.

In determining whether a reference discloses an invention so as to anticipate it, the law requires that the reference be compared to the patent claim at issue. *In re Paulsen*, 30 F.3d 1475 (Fed. Cir. 1994) (every limitation of the claimed invention must be disclosed in the prior art reference). As previously noted and pertinent in this regard, the ALJ adopted an expansive and

subjective claim construction; as the ALJ determined, "none of said claims (1) specify . . . what specific base or specific solvent is used with the 'controlled amount of protic material,' (2) define 'controlled amount' . . . or (8) specify any selectivity in products as it relates to the claimed term 'controlled amount of protic material.'" (ID at 49-50.)

The ALJ then committed clear legal error when he later concluded, directly contrary to his broad claim interpretation, that Wohl did not control the amount of protic material because "he *evaporated all of the water* from his reaction and *did not maintain the minimum amount of selectivity* of the desired 4-ADPA intermediate." (ID at 111-12.) First, this reasoning ignores the explicit statement in the patent itself, from the PARAGRAPH, that "the present reaction could be conducted under *anhydrous conditions*," *i.e.*, without water. (Ex. 1, col. 4, lines 46-48; ID at 59.) In other words, the "minimum" can be no water. Second, Flexsys' own inventor-expert witness (Bashkin) agreed that Wohl maintained control over protic material during the course of the aniline-nitrobenzene reaction. (Ex. 4, Tr. 2117-2119.) Third, the fact that Wohl got low selectivity for the "desired" para-product cannot possibly support the ALJ's determination that Wohl does not teach steps (a) and (b) of the asserted patent claims, given the ALJ's determination that the claims are so broad that they do not "specify any selectivity in products." (ID at 50.)

Flexsys admitted that Wohl reports the production of a 4-ADPA intermediate by combining aniline and nitrobenzene; Flexsys' expert so admitted under cross-examination at the hearing. (Ex. 3 at FA030986; Ex. 4, Tr. 2116.) The other evidence was also compelling on this point (Ex. 1, col. 3, lines 48-52; Ex. 4, Tr. 325:12-326:8; 776:15-17; 1902:18-1903:1; 1944:7-24.) Nonetheless, the ALJ incorrectly determined that Wohl "does not disclose that the nitrobenzene and aniline react with one another to produce [4-ADPA intermediates]." (ID at

110.) Also, the ALJ seems to have wrongfully accepted the proposition that the inventors named on the '063 patent, Stern and Bashkin, had "discovered" a "novel reaction" of aniline, nitrobenzene, and base to form 4-ADPA intermediates. (ID at 21.) However, before the subject patents were published, a reviewer in the field of classical synthetic organic chemistry (Ex. 8, corresponding to RX 857, SCS014061 and 014063; Ex. 9, corresponding to RX 857A) identified – and quoted – the 1903 Wohl process as the accepted published route to form the 4-nitroso intermediate of 4-ADPA directly from aniline and nitrobenzene in the presence of sodium hydroxide (NaOH) as base. (Ex. 8 at SCS014063, n.1; Ex. 4, Tr. 1870:7-16.) The ALJ ignored this evidence[15] on the understanding of Wohl in the art, making the ALJ's apparent finding that Wohl could not be understood to disclose a reaction of aniline and nitrobenzene only by improper "hindsight" analysis (ID at 110) clearly erroneous. The ALJ's finding that Wohl does not describe steps (a) and (b) of the asserted claims is unfounded in view of the understanding of the disclosure of Wohl by unbiased academics.

Equally important, Monsanto *admitted* during prosecution before the USPTO that Wohl (1) discloses "the reaction of aniline with nitrobenzene in aniline solvent using NaOH as base under 'anhydrous' conditions" and (2) identifies a "product of this reaction of aniline with nitrobenzene as p-nitrosodiphenylamine." (Ex. 3 at FA030986.) Such an admission during prosecution is "binding" on Monsanto-Flexsys and it was further legal error for the ALJ to

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[15] The Welcher 1947 text is prior art (Ex. 8 at SCS014063). The 1992 *Manual of Organic Synthesis* refers to that prior art (Ex. 8 at SCS014062, n.2) and attaches the pertinent portions (Ex. 8 at SCS014063). While the *Manual* itself is not technically prior art, it is a "later publication" that is properly considered as "evidence of the state of the art exiting on the filing date of an application." *In re Donohue*, 632 F.2d 123,126 (C.C.P.A. 1980); *see also Plant Genetic Sys. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003); *In re Hogan*, 559 F.2d 595, 605 (C.C.P.A. 1977) (citing *In re Wilson*, 311 F.2d 266 (C.C.P.A. 1962)).

ignore this binding admission. *Springs Window Fashions, LP v. Novo Indus. LP*, 323 F.3d 989, 995 (Fed. Cir. 2003) ("The public notice function of a patent and its prosecution history requires that a patentee be held to what he declares during the prosecution of his patent); *Digital Biometrics, Inc. v. Identix, Inc.*, 149 F.3d 1335 (Fed. Cir. 1998) ("definitive statements made during prosecution" are binding); *Tyler Refrigeration v. Kysor Indus. Corp.*, 777 F.2d 687, 690 (Fed. Cir. 1985). Moreover, using the same expansive claim construction adopted by the ALJ (ID at 49-50), *i.e.*, that the asserted claims do not require any specific yield or selectivity, the European Patent Office and the Korean courts – all of the other tribunals ruling on the novelty of the subject matter of steps (a) and (b) of the asserted claims – uniformly and correctly found claims corresponding to steps (a) and (b) of the asserted claims to be fully described or anticipated by Wohl.[16] (Ex. 5, corresponding to RX 835, at FA008913 at X and FA008914 at 2.1 and 2.2 re E1 (the 1903 Wohl paper); Ex. 6, corresponding to RX847, at 09135T and 09148T; and Ex. 7, corresponding to RX848, at 09159T at (2) and 09168T at (C).)

The ALJ's evidentiary conclusion that Wohl "wanted to maintain anhydrous conditions to get nitrobenzene to react with NaOH" (ID at 113) is nowhere stated in Wohl; nor is that conclusion supported by the cited testimony of inventor/expert witness Bashkin (Ex. 4, Tr. 331). Also, the ALJ's impermissible decision – given the prior admission to the contrary during prosecution to the USPTO – that Wohl does not teach the reaction of aniline and nitrobenzene to form 4-nitrosodiphenylamine seems to be based, at least in part, on the legally improper conclusion that Wohl did not understand the exact mechanism by which nitrobenzene and aniline

[16] The ITC Staff also reached this same conclusion after the hearing and so stated in its Post Hearing Briefs.

react "in the presence of a suitable base," NaOH in Wohl's case. Wohl may have misunderstood the mechanism and the Monsanto inventors may or may not have gotten it right (Ex. 4, Tr. 537:25-538:22; 2056:1-2057:13). But all that is legally irrelevant. The patents themselves neither disclose nor claim any particular reaction mechanism. (Ex. 4, Tr. 438:14-20.) The law is clear on this point: "the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render [an] old composition patentability new to the discoverer." *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347 (Fed. Cir. 1999); *see also Verdegaal Bros., Inc. v. Union Oil Co.*, 814 F.2d 628, 630 (Fed. Cir. 1987). So it does not matter whether or not Drs. Stern or Bashkin were the first to correctly understand how the Wohl reaction of aniline and nitrobenzene worked.[17]

The ALJ found that Wohl does not teach a "suitable solvent system." (ID at 111.) This conclusion was contrary to Flexsys' representations to the PTO during prosecution. This conclusion is also contrary to the explanation in the patent itself, which expressly teaches that aniline in molar excess over nitrobenzene is the *preferred* "suitable solvent system." (Ex. 1, col. 3, lines 42-43.) Flexsys' expert witness did not dispute at trial that Wohl employed a "suitable solvent system." (Ex. 4, Tr. 1010) (a solvent system is suitable if it brings nitrobenzene and aniline into reactive contact so that they can react.) Moreover, Flexsys' witnesses admitted that Wohl used aniline in 30% excess over nitrobenzene (Ex. 4, Tr. 381:11-15; 434:7-17; 437:11-18; 466:17-467:11; 596:12-24; 777:11-16; 1871:6-1872:5; 1902:18-1907:4; 1984:23-1998:20;

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[17] Even the ALJ expressly recognized this earlier in his decision. (ID at 33) (claiming he was not relying on the inventors' expression of the mechanism "for any anticipation" but solely "in support of the technical prong of the domestic industry argument"). But the ALJ conveniently and erroneously failed to apply this rule when he arrived at the invalidity section of the ID.

2114-16.), which the patent defines as the *preferred* solvent system. Also, it was undisputed at trial that there is even less aniline relative to nitrobenzene in Example 3 than in the published Wohl experiment. (Ex. 4, Tr. 777:22-778:24.) And, as explained above, Flexsys told the Patent Office that Wohl used aniline as the solvent. (Ex. 1, col. 3, lines 41-43, col. 4, lines 28-32; Ex. 3 at 7; Ex. 4, Tr. 777:11-16; 779:12-22; 1941:7-1942:6.) Again, it was legally impermissible for the ALJ to ignore that binding admission on this point.

Wohl discloses a process that meets all the limitations of steps (a) and (b) of the four asserted claims. It would have been obvious to those skilled in the art in 1990 to combine the Wohl process with the then-existing commercial reduction and alkylation steps for producing 4-ADPA and 6PPD, particularly since the patent claims are not limited to a process that produces 4-ADPA intermediates in high yield or selectivity.

The asserted claims of the '111 patent add only the well known concept that control of the amount of protic material was accomplished by continuous distillation. Indeed, Wohl described such continuous distillation to remove water by operating at 120°C. Also, continuous distillation was a well known method to remove a reaction product of the coupling reaction (water) and drive the coupling reaction to higher yields according to the Law of Mass Action. Thus, the asserted claims of the '111 patent were also plainly obvious for these additional reasons.

C. Secondary Considerations Do Not Support Nonobviousness

To bolster his unsupported validity conclusion, the ALJ found, as the only "objective indicia of nonobviousness," purported commercial success, based on the expenditure of money by Monsanto and Flexsys to build the pilot plant and then the commercial plant. (ID at 113-14.)

This expenditure of money was the only evidence of any secondary consideration relied upon in the ID.

The ALJ's reliance solely on money invested by the patentee was improper, as a matter of law. Under some circumstances, commercial success may be a secondary indicator of nonobviousness. However, the type of success that is viewed as supporting nonobviousness is not merely the amount of money spent by the patentee to commercialize the invention, but rather the results obtained in the marketplace that show "success" correlated to the invention. *Kansas Jack, Inc. v. Kuhn*, 719 F.2d 1144, 1151 (Fed. Cir. 1983); *see also Cable Elec. Prods., Inc, v. Genmark, Inc.*, 770 F.2d 1015 (Fed. Cir. 1985); *In re Baxter Travenol Labs.*, 952 F.2d 388 (Fed. Cir. 1991); *Tennant Co. v. Hako Minuteman Inc.*, 22 U.S.P.Q.2d 1161, 1177 (N.D. Ill. 1991) (*citing Demaco Corp. v. F. von Langsdorff Licensing Ltd.*, 851 F.2d 1387 (Fed. Cir. 1988)). The fact that a patentee had sunk a large amount of money into commercializing the invention could equally well show that the patentee had undeserved faith in the invention, had bad business judgment, or could have been based on any number of other irrelevant considerations. In no case does the mere investment of money alone demonstrate commercial success that evidences nonobviousness.

The ALJ committed clear legal error in *not* holding claims 30 and 61 of the '063 patent and claims 7 and 11 of the '111 patent invalid as obvious over the Wohl 1903 paper combined with the well known three steps of the prior art commercial processes.

VII. THERE IS NO INFRINGEMENT OF THE PROPERLY CONSTRUED CLAIMS

A. The Asserted Claims, As Properly Construed, Are Not Literally Infringed

It is uncontroverted that, if the claim term "controlled amount" of protic material is construed in accordance with the express definition in the patents, there is no literal

infringement. That express definition requires that the water content must be less than about 4%, when aniline is the solvent. [[

]] The Sinorgchem process is a classic case of a party properly relying on an express definition in a patent to develop a new, innovative, noninfringing process of its own.[18] Sinorgchem does not infringe any of the asserted claims, because it does not practice every element of the claims, as properly construed. *Strattec Sec. Corp. v. Gen. Auto Specialty Co., Inc.*, 126 F.3d 1411, 1418 (Fed. Cir. 1997).

The ALJ's conclusion of infringement further illustrates the error of the claim construction. The ALJ concludes, with little analysis, that Sinorgchem's [[ ]] process literally meets the "controlled amount" of protic material claim limitation as construed by the ALJ. (ID at 99-102.) But the ID never ties the Sinorgchem process to the proffered claim construction or analyzes how Sinorgchem's process controls the protic material between an upper limit and a lower limit. The ID is completely silent with regard to how Sinorgchem's alleged "controlled amount" of protic material relates to inhibition and selectivity: the two terms the ALJ found key to the claim construction. The ALJ conclusion of infringement, without such explanation, is unfounded and further demonstrates the legal error of a claim construction that ignores the express definition in the patents.

Under the ALJ's erroneous claim construction, as long as a process "works" to produce 4-ADPA, it infringes; according to the ID, no analysis of the inhibition or the selectivity of the accused process is appropriate or necessary. Such conclusions are clearly wrong.

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[18] As described in sections II and VI, *supra*, the reaction of aniline and nitrobenzene in the presence of a base to produce the 4-ADPA intermediate, 4-NODPA, was not invented by Flexsys.

B. The Asserted Claims, As Properly Construed, Are Not Infringed Under The Doctrine Of Equivalents

The ALJ did not reach the issue of infringement under the doctrine of equivalents. In the event that the Commission concludes there is no literal infringement, there should also be no infringement under the doctrine of equivalents.

If the claims are properly construed to account for the express definition, Sinorgchem's process does not infringe under the doctrine of equivalents for at least three independent reasons:

- Flexsys disavowed claim coverage for processes having more than about 4% water, when aniline is the solvent;
- the doctrine of equivalents cannot be used to "vitiate" the claim term "controlled amount of protic material"; and
- [[

]]

On the issue of infringement under the doctrine of equivalents, Sinorgchem further relies on the arguments made in the Post-Hearing Reply Brief of Respondents at 41-51 (Ex. 15) and on the Post-Hearing Brief of Respondents at 27-30 (Ex. 16).

[[

]] The Sinorgchem process is not equivalent to the process of the asserted patent claims.

In sum, the Commission should review the ID and find that, as a matter of law, there is no direct infringement, literal or under the doctrine of equivalents, by Sinorgchem. 35 U.S.C. § 271(a). Sovereign, being solely a purchaser and importer of Sinorgchem's 6PPD, likewise does not directly infringe. In addition, since there is no direct infringement, there is no indirect

infringement of any Respondent. 35 U.S.C. § 271(b) and (c). *Dynacor Holdings Corp. v. U.S. Philips Corp.*, 363 F.3d 1263, 1274 (Fed. Cir. 2004).

VIII. FLEXSYS CANNOT ESTABLISH THE TECHNICAL PRONG OF DOMESTIC INDUSTRY IF THE CLAIMS ARE PROPERLY CONSTRUED

If the claims are properly construed to consider the express definition, Flexsys does not practice any of the asserted claims of the '063 and '111 patents; its process does not satisfy the claim limitation of a "controlled amount" of protic material. There is no dispute that the Flexsys process – as implemented in the Antwerp plant – couples aniline and nitrobenzene in the presence of the base, TMAH, with aniline as the solvent. (ID at 120-21.) There is equally no dispute that the water content of Flexsys' process is approximately 8.5% at the end of the coupling reaction, when aniline is the solvent. (ID at 121.) Therefore, in view of the "up to about 4% H2O" limitation in the asserted patents (when aniline is the solvent), the conclusion is unmistakable that Flexsys does not meet the technical prong of the domestic industry requirement, because its process does not practice any of the asserted claims.

IX. CONCLUSION

For the foregoing reasons, Respondents Sinorgchem and Sovereign submit that their Petition for Review of the ID issued on February 17, 2006 be granted and that Sinorgchem and Sovereign be found not to have violated Section 337. Flexsys is not entitled to any relief.

Dated: March 13, 2006

Respectfully submitted,

Marcia H. Sundeen /zz

Marcia H. Sundeen
1700 Pennsylvania Avenue, N.W. Suite 400
Washington, DC 20006
Telephone: (202) 349-3673

Stanton T. Lawrence, III
Paul J. Zegger
Zhiqiang Zhao
Arnold & Porter LLP
555 Twelfth Street, NW
Washington, DC 20004
Telephone: (202) 942-5060

Jiabin Wang
Shanlon Wu
King and Wood PRC Lawyers
31st Floor, Tower A, Jianwai SOHO,
39 Dongsanhuan Zhonglu
Chaoyang District, Beijing 100022
People's Republic of China

Manni Li
Venable LLP
575 7th Street, NW
Washington, DC 20004
Telephone: (202) 344-8119

Counsel for Sinorgchem Co., Shandong

James K. Kearney
Womble Carlyle Sandridge & Rice LLP
1401 I Street, N.W., 7th Floor
Washington, DC 20005
Telephone: (202) 857-4400

Deborah A. Coleman
Hahn Loeser & Parks LLP
3300 BP Tower
200 Public Square
Cleveland, Ohio 44114
Telephone: (216) 621-0150

Scott M. Oldham
John J. Cunniff
Hahn Loeser & Parks LLP
One GOJO Plaza, Suite 300
501 S. Main Street
Akron, Ohio 44311
Telephone: (330) 864-5550

Nanda K. Alapati
Womble Carlyle Sandridge & Rice LLP
8065 Leesburg Pike, 4th Floor
Tysons Corner, Virginia 22182
Telephone: (703) 790-3310

Counsel for Sovereign Chemical Company

UNITED STATES INTERNATIONAL TRADE COMMISSION
WASHINGTON, D.C.

Before the Honorable Paul J. Luckern

In the Matter of	
CERTAIN RUBBER ANTIDEGRADANTS, COMPONENTS THEREOF, AND PRODUCTS CONTAINING SAME	Investigation No. 337-TA-533

EXHIBITS TO PETITION FOR REVIEW OF RESPONDENTS SINORGCHEM CO., SHANDONG AND SOVEREIGN CHEMICAL COMPANY OF FEBRUARY 17, 2006 FINAL INITIAL AND RECOMMENDED DETERMINATIONS

Marcia H. Sundeen
1700 Pennsylvania Avenue, N.W. Suite 400
Washington, D.C. 20006
Telephone: (202) 349-3673

Stanton T. Lawrence, III
Paul J. Zegger
Zhiqiang Zhao
Arnold & Porter LLP
555 Twelfth Street, NW
Washington, DC 20004
Telephone: (202) 942-5060

Jiabin Wang
Shanlon Wu
King and Wood PRC Lawyers
31st Floor, Tower A, Jianwai SOHO,
39 Dongsanhuan Zhonglu
Chaoyang District, Beijing 100022
People's Republic of China

Manni Li
Venable LLP
575 7th Street, NW
Washington, DC 20004
Telephone: (202) 344-8119

Counsel for Sinorgchem Co., Shandong

James K. Kearney
Womble Carlyle Sandridge & Rice LLP
1401 I Street, N.W., 7th Floor
Washington, DC 20005
Telephone: (202) 857-4400

Deborah A. Coleman
Hahn Loeser & Parks LLP
3300 BP Tower
200 Public Square
Cleveland, Ohio 44114
Telephone: (216) 621-0150

Scott M. Oldham
John J. Cunniff
Hahn Loeser & Parks LLP
One GOJO Plaza, Suite 300
501 S. Main Street
Akron, Ohio 44311
Telephone: (330) 864-5550

Nanda K. Alapati
Womble Carlyle Sandridge & Rice LLP
8065 Leesburg Pike, 4th Floor
Tysons Corner, Virginia 22182
Telephone: (703) 790-3310

Counsel for Sovereign Chemical Company

Dated March 3, 2006

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EXHIBITS TO PETITION FOR REVIEW OF RESPONDENTS SINORGCHEM CO., SHANDONG AND SOVEREIGN CHEMICAL COMPANY OF FEBRUARY 17, 2006 FINAL INITIAL AND RECOMMENDED DETERMINATIONS

Ex. 1	United States Patent No. 5,117,063 (the "'063 Patent") (CX-1)
Ex. 2	United States Patent No. 5,608,111 (the "'111 Patent") (CX-3)
Ex. 3	May 5, 1995 Preliminary Amendment from Prosecution History of '111 Patent (CX-4, FAO30980-91)
Ex. 4	Excerpts from Hearing Transcript
Ex. 5	6/16/2000 EPO Decision Revoking European Patent No. 590053(RX-835)
Ex. 6	10/4/2005 Decision of the Korean Intellectual Property Tribunal (RX-847) (Translation)
Ex. 7	10/12/2005 Seoul Superior Court Judgment (RX-848)(Translation)
Ex. 8	Manual of Organic Synthesis, Beijing Institute of Technology (1992) (with Translation) (RX-857)
Ex. 9	Welcher, F.J., Organic Analytical Reagents, vol. 3 (1947) (RX-857A)
Ex. 10	*Abbott Labs. v. Teva Pharms. USA, Inc.*, 2005 WL 1026746 (D. Del. April 22, 2005)
Ex. 11	"Importance of Controlling Protic Material (e.g., Water), Example 3: When Aniline is a Solvent (RDX-1)
Ex. 12	United States Patent Application Pub. No. 2005/0065376 A1 (RX-707)
Ex. 13	Flexsys Post-Hearing Brief at 3
Ex. 14	Chart of Data in Example 8 of the '063 and '111 Patents
Ex. 15	Post-Hearing Brief of Respondents at 41-51 (Doctrine of Equivalents)
Ex. 16	Post-Hearing Reply Brief of Respondents at 27-30 (Doctrine of Equivalents)
Ex. 17	Post-Hearing Brief of Commission Investigative Staff at 38
Ex. 18	A. Wohl: Relating to the Reaction Between Nitrobenzene and Aniline in the Presence of Alkali (November 23, 1903) (RX-9; RX-43)

U 1275389

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

January 24, 2005

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *5,117,063*
ISSUE DATE: *May 26, 1992*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

L. Edelen

L. EDELEN
Certifying Officer

EXHIBIT
tabbies
CX 1
FlexSys

US005117063A

United States Patent [19]

Stern et al.

[11] Patent Number: 5,117,063

[45] Date of Patent: May 26, 1992

[54] METHOD OF PREPARING 4-AMINODIPHENYLAMINE

[75] Inventors: Michael K. Stern; James K. Bashkin, both of University City, Mo.

[73] Assignee: Monsanto Company, St. Louis, Mo.

[21] Appl. No.: 719,876

[22] Filed: Jun. 21, 1991

[51] Int. Cl.[5] C07C 209/02; C07C 209/26; C07C 209/36; C07C 209/38

[52] U.S. Cl. 564/398; 564/397; 564/408; 564/420; 564/421; 564/423; 564/433; 564/434

[58] Field of Search 564/397, 398, 408, 420, 564/421, 422, 423

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Primary Examiner—Richard L. Raymond

Attorney, Agent, or Firm—Charles E. Smith; Paul L. Passley; James C. Bolding

[57] ABSTRACT

A method of producing 4-ADPA is disclosed wherein aniline and nitrobenzene are reacted under suitable conditions to produce 4-nitrodiphenylamine and/or 4-nitrosodiphenylamine and/or their salts, either or both of which are subsequently reduced to produce 4-ADPA. The 4-ADPA can be reductively alkylated to produce p-phenylenediamine products which are useful as antiozonants.

94 Claims, No Drawings

METHOD OF PREPARING 4-AMINODIPHENYLAMINE

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to methods for preparing 4-aminodiphenylamine (4-ADPA) and, more particularly, relates to a method for preparing 4-ADPA wherein aniline is reacted with nitrobenzene in the presence of a base, and under conditions wherein the amount of protic material, e.g., water, is controlled, to produce a mixture rich in the salt of 4-nitrodiphenylamine and/or the salt of 4-nitrosodiphenylamine. The 4-nitrodiphenylamine and/or 4-nitrosodiphenylamine salts are isolated and subsequently hydrogenated or, alternatively, the reaction mixture itself is hydrogenated, to produce 4-ADPA in high yield. The present invention also relates to methods for preparing 4-ADPA intermediates as well as to alkylated p-phenylenediamine products useful as antioxidants.

2. Related Art

It is known to prepare 4-ADPA by way of a nucleophilic aromatic substitution mechanism, wherein an aniline derivative replaces halide. This method involves preparation of a 4-ADPA intermediate, namely 4-nitrodiphenylamine (4-NDPA) followed by reduction of the nitro moiety. The 4-NDPA is prepared by reacting p-chloronitrobenzene with an aniline derivative, such as formanilide or an alkali metal salt thereof, in the presence of an acid acceptor or neutralizing agent, such as potassium carbonate, and, optionally, utilizing a catalyst. See, for example, U.S. Pat. Nos. 4,187,248; 4,683,332; 4,155,936; 4,670,595; 4,122,118; 4,614,817; 4,209,463; 4,196,146; 4,187,249; 4,140,716. This method is disadvantageous in that the halide that is displaced is corrosive to the reactors and appears in the waste stream and must therefore be disposed of at considerable expense. Furthermore, use of an aniline derivative such as formanilide, and use of p-chloro-nitrobenzene, requires additional manufacturing equipment and capabilities to produce such starting materials from aniline and nitrobenzene, respectively.

It is also known to prepare 4-ADPA from the head-to-tail coupling of aniline. See, for example, G.B. 1,440,767 and U.S. Pat. No. 4,760,186. This method is disadvantageous in that the yield of 4-ADPA is not acceptable for a commercial process. It is also known to decarboxylate a urethane to produce 4-NDPA. See U.S. Pat. No. 3,847,990. However, such method is not commercially practical in terms of cost and yield.

It is known to prepare 4-ADPA by hydrogenating p-nitrosodiphenylhydroxylamine which can be prepared by catalytic reduction of nitrosobenzene utilizing, as a reducing agent, aliphatic compounds, benzene, naphthalene or ethylenically unsaturated compounds. See, for example, U.S. Pat. Nos. 4,178,315 and 4,404,401. It is also known to prepare p-nitrosodiphenylamine from diphenylamine and an alkyl nitrate in the presence of excess hydrogen chloride. See, for example, U.S. Pat. Nos. 4,518,803 and 4,479,008.

It is also known to produce 4-nitrosodiphenylamine by reacting acetanilide and nitrobenzene in DMSO in the presence of sodium hydroxide and potassium carbonate at 80° C. for 5 hours. See Ayyangar et al., Tetrahedron Letters, Vol. 31, No. 22, pp. 3217–3220 (1990). See also, Wohl, Chemische Berichte, 36, p. 4135 (1903) and Chemische Berichte, 34, p. 2442 (1901). However, the yield of 4-nitrosodiphenylamine is low and is therefore not commercially practical. Furthermore, such method requires utilization of an aniline derivative, namely, acetanilide, and therefore increases the cost of the starting materials.

The process of the present invention does not include a halide source and therefore eliminates the expensive halide removal from the waste stream. In addition, the process of the present invention is much less expensive in terms of manufacturing costs, as well as the cost of raw materials, because instead of the derivatives of aniline and nitrobenzene, the present method utilizes aniline and nitrobenzene directly.

SUMMARY OF THE INVENTION

The present invention is directed to a method of preparing 4-ADPA intermediates, namely 4-nitrodiphenylamine (4-NDPA) and the salts thereof, and/or 4-nitrosodiphenylamine (p-NDPA) and/or the salts thereof, wherein aniline and nitrobenzene are brought into reactive contact in a suitable solvent system, and then reacted in the presence of a base and under conditions wherein the amount of protic material, such as water, is controlled. The resulting reaction mixture is rich in 4-ADPA intermediates, including the 4-nitrodiphenylamine and/or 4-nitrosodiphenylamine salts. The process can be utilized according to the teachings of the present invention to produce a high yield of the 4-nitroso product (p-nitrosodiphenylamine and its salt) with little or no 4-nitro product. The 4-nitroso reaction product mixture can then be hydrogenated directly, or the 4-nitroso product can then be isolated and subsequently hydrogenated, to produce 4-ADPA in high yield. Similarly, the 4-nitro product (4-nitrodiphenylamine and its salt) can be produced in high yield with little or no 4-nitroso product, and the 4-nitro product, or the isolated 4-nitro product, can be hydrogenated to produce 4-ADPA in high yield. Alternatively, the 4-nitro and 4-nitroso products are both produced and are not isolated but the reaction mixture is hydrogenated directly to produce 4-ADPA. The resulting 4-ADPA can be utilized to prepare alkylated products of p-phenylenediamine, which products are useful as antioxidants and antiozonants. Alternatively, the 4-ADPA intermediates can be reduced and the reduced material alkylated in the same reaction vessel utilizing a ketone as a solvent.

DETAILED DESCRIPTION OF THE INVENTION

The subject method for producing 4-ADPA intermediates involves the steps of:

a) bringing aniline and nitrobenzene into reactive contact in a suitable solvent system;

b) reacting the aniline and nitrobenzene in a confined zone, such as a reactor, at a suitable temperature and in the presence of a suitable base and a controlled amount of protic material, such as water, to produce 4-nitrodiphenylamine and its salt and/or 4-nitrosodiphenylamine and its salt.

For producing 4-ADPA, the subject method includes the following step:

c) reducing the 4-nitrosodiphenylamine and its salt and/or the 4-nitrodiphenylamine and its salt to produce 4-ADPA.

For producing alkylated p-phenylenediamines, the subject method includes the step of:

d) reductively alkylating the 4-ADPA of Step c).

As utilized herein, the term "4-ADPA intermediates" means 4-nitrodiphenylamine, 4-nitrosodiphenylamine (also referred to as p-nitrosodiphenylamine) and the salts thereof. Thus, reference to "one or more 4-ADPA intermediates" refers to one or both of the neutral compounds, i.e., those that are not in the form of a salt, and/or the salt of one or both of such compounds. The salt is produced in the reaction mixture from reaction of the 4-nitro and/or 4-nitroso products with the base. Thus, the reaction mixture produced in the method of the present invention can include one of the compounds or salts or any combination thereof depending on the specific reaction conditions selected.

The molar ratio of aniline to nitrobenzene can vary from a large excess of nitrobenzene to a large excess of aniline. Preferably, the reaction is conducted utilizing an excess of aniline. The ratio of 4-nitro to 4-nitroso produced in the reaction of the present invention can be controlled by varying the ratio of aniline to nitrobenzene. The higher the ratio of aniline to nitrobenzene, the higher the ratio of 4-nitroso to 4-nitro. Conversely, the higher the ratio of nitrobenzene to aniline, the higher the ratio of 4-nitro to 4-nitroso.

Azobenzene is also produced in this reaction in variable quantities depending on the reaction conditions. One way of controlling azobenzene production is through the ratio of aniline to nitrobenzene. Thus, as this ratio is increased, the amount of azobenzene generally decreases. As discussed below, and as illustrated in the Examples set forth below, other variables, such as the amount of base and oxygen, can also affect the amount of azobenzene produced. Thus, utilizing the teachings of the present invention, one skilled in the art can conduct the reaction of the present invention to control the amount of azobenzene that is produced.

Suitable solvent systems include, but are not limited to, solvents such as, for example, dimethylsulfoxide, N-methylpyrolidone, dimethylformamide, aniline, pyridine, nitrobenzene and the like, as well as mixtures thereof. Preferably, aniline is used in excess in the reaction as stated above, and the aniline in excess of the molar amount of nitrobenzene serves as the solvent. As described in more detail below, solvent mixtures can be utilized wherein one or more of the suitable solvents and another solvent, such as a controlled amount of a protic solvent, e.g., methanol, are combined.

Suitable bases include, but are not limited to, organic and inorganic bases such as, for example, alkali metals, such as sodium metal, alkali metal hydrides, hydroxides and alkoxides, such as sodium hydride, lithium hydroxide, sodium hydroxide, cesium hydroxide, potassium hydroxide, potassium t-butoxide, and the like, including mixtures thereof. Other acceptable base materials include, but are not limited to, phase transfer catalysts in conjunction with a suitable base source such as tetraalkylammonium hydroxides, e.g., tetramethylammonium hydroxide, and other combinations of phase transfer catalysts and suitable bases such as suitable bases in conjunction with aryl ammonium salts, crown ethers and the like, and amine bases, such as lithium bis(trimethylsilyl) amide, and the like, including mixtures thereof. Preferred materials (bases) for use as bases are tetraalkylammonium hydroxides such as tetramethylammonium hydroxide. Preferably, the base is added to the aniline to produce a mixture which is then combined with the nitrobenzene. Alternatively, the base can be added after the aniline and nitrobenzene have been combined. Addition of materials can be above or below surface addition. The amount of base utilized in the present process can vary over a wide range. For example, the reaction can be conducted in a manner which is limiting in base or the reaction can be conducted in a manner which is limiting in nitrobenzene or aniline depending, among other factors, on the desired degree of minimization of azobenzene.

The reaction is conducted at a suitable temperature which can vary over a wide range. For example, the temperature can fall within a range of from about −10° C. to about 150° C., such as from about 0° C. to about 100° C., preferably from about 10° C. to about 80° C. A most preferred temperature for conducting the reaction of the present invention is from about 40° C. to about 70° C., such as at 50° C. Where aniline is utilized as the solvent under aerobic reaction conditions, as the temperature of the reaction increases, the amount of azobenzene produced increases. However, where the reaction is conducted in aniline under anaerobic conditions, higher temperatures do not necessarily increase the amount of azobenzene. Where production of azobenzene is not a problem, higher temperatures will be suitable. However, where it is desired to minimize the amount of azobenzene, lower temperatures or anaerobic reaction conditions are more suitable. Alternatively, to minimize the amount of azobenzene while conducting the reaction at higher temperatures, a solvent other than aniline can be used and the ratio of aniline to nitrobenzene can be controlled.

Control of the amount of protic material present in the reaction is important. Generally, when the reaction is conducted in aniline, water present in the reaction in an amount greater than about 4% H_2O, (based on volume of the reaction mixture) inhibits the reaction of the aniline with the nitrobenzene to an extent where the reaction is no longer significant. Reducing the amount of water to below the 4% level causes the reaction to proceed in an acceptable manner. When tetramethylammonium hydroxide is utilized as a base with aniline as the solvent, as the amount of water is reduced further, e.g., down to about 0.5% based on the volume of the reaction mixture, the total amount of 4-nitrodiphenylamine and 4-nitrosodiphenylamine increases with some loss in selectivity so that more 2-nitrodiphenylamine is produced but still in minor amounts. Thus, the present reaction could be conducted under anhydrous conditions. A "controlled amount" of protic material is an amount up to that which inhibits the reaction of aniline with nitrobenzene, e.g., up to about 4% H_2O based on the volume of the reaction mixture when aniline is utilized as the solvent. The upper limit for the amount of protic material present in the reaction varies with the solvent. For example, when DMSO is utilized as the solvent and tetramethylammonium hydroxide is utilized as the base, the upper limit on the amount of protic material present in the reaction is about 8% H_2O based on the volume of the reaction mixture. When aniline is utilized as a solvent with the same base, the upper limit is 4% H_2O based on the volume of the reaction mixture. In addition, the amount of protic material tolerated will vary with type of base, amount of base, and base cation, used in the various solvent systems. However, it is within the skill of one in the art, utilizing the teachings of the present invention, to determine the specific upper limit of the amount of protic material for a specific solvent, type and amount of base, base cation and the like. The minimum amount of protic material necessary

to maintain selectivity of the desired products will also depend on the solvent, type and amount of base, base cation and the like, that is utilized and can also be determined by one skilled in the art.

Since the amount of protic material present in the reaction is important, it is preferred to reduce the amount of protic material present as much as possible and then add back to the reaction the desired amount, e.g., 0.5 vol. % when aniline is used as the solvent. Protic materials that can be utilized to add back to the reaction are known to those skilled in the art and include, but are not limited to, water, methanol and the like. Methods for measuring the amount of protic material and for reducing the amount of protic material as much as possible are well known in the art. For example, the amount of water present in certain reagents can be determined by utilizing a Karl-Fischer apparatus, and the amount of water can be reduced through distillation and/or drying under reduced pressure, drying in the presence of P_2O_5 and other agents, azeotropic distillation utilizing, for example, aniline, and the like, including combinations thereof.

The reaction can be conducted under aerobic or anaerobic conditions. Under aerobic conditions, the reaction is conducted essentially as described above in a reaction zone which is exposed to oxygen, usually by exposure to air. Under aerobic conditions, the pressure at which the reaction is conducted can vary and the optimal pressure, as well as the optimal combination of pressure and temperature/pressure conditions, are easily determined by one skilled in the art. For example, the reaction can be conducted at room temperature and at a pressure ranging from about 10 psig to about 250 psig, such as from about 14 to about 150 psig. Under anaerobic conditions, the reaction can be conducted at atmospheric pressure or reduced or increased pressures, in the presence of a neutral gas such as, for example, nitrogen or argon. Optimal conditions for a particular set of reaction parameters, such as temperature, base, solvent and the like, are easily determined by one skilled in the art utilizing the teachings of the present invention. It has been observed that less azobenzene is produced when the reaction is conducted anaerobically with aniline as the solvent. It has also been observed that less azobenzene is produced when the reaction is conducted aerobically with DMSO, and other similar solvents, as the solvent.

The 4-nitrodiphenylamine and/or 4-nitrosodiphenylamine and/or their salts can be reduced to 4-ADPA. The neutral compounds can be generated from the salts utilizing water and/or an acid. See, for example, Example 1D. Alternatively, the salts can be reduced as shown in Example 1A. This reduction can be carried out by any of many known reductive processes, such as using a hydride source, e.g., sodium borohydride in conjunction with palladium- or platinum-on-carbon catalyst. Preferably, this reduction is conducted by a catalytic reduction wherein hydrogenation is effected under hydrogen pressure in the presence of platinum- or palladium-on-carbon, nickel, and the like. This hydrogenation process is described in detail in "Catalytic Hydrogenation in Organic Synthesis", P. N. Rylander, Academic Press, N.Y., p. 299 (1979), which is hereby incorporated herein by reference. Preferably, the hydrogenation is conducted utilizing a platinum-on-carbon catalyst in a suitable solvent such as, for example, either xylene or aniline, mixtures thereof, or mixtures which include water as the solvent and a hydrogen pressure of from 100 psig H_2 to about 340 psig H_2 at a temperature of about 80° C.

Reductive alkylation of 4-ADPA to produce antiozonants can be conducted by any one of several well known methods. See, for example, U.S. Pat. No. 4,900,868. Preferably, 4-ADPA and a suitable ketone or aldehyde are reacted in the presence of hydrogen and platinum on carbon as catalyst. Suitable ketones include methylisobutyl ketone (MIBK), acetone, methylisoamylketone and 2-octanone. It should be noted that reduction of the 4-ADPA intermediates and alkylation of the reduced material can be conducted in the same reaction vessel utilizing the ketone as a solvent. See, for example, U.S. Pat. No. 4,463,191, and Banerjee et al, J. Chem. Soc. Chem. Comm. 18, 1275-76 (1988).

Contemplated equivalents of the reactants and reagents set forth above are reactants and reagents otherwise corresponding thereto and having the same general properties wherein one or more of the various groups, e.g., NO_2, are simple variations. In addition, where a substituent is designated as, or can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position is not critical so long as it does not adversely affect the overall activity and/or synthesis procedure.

The chemical reactions described above are generally disclosed in terms of their broadest application to the method of this invention. Occasionally, the reaction conditions may not be applicable as specifically described to each reactant and reagent within the disclosed scope. For example, certain suitable bases may not be as soluble in one solvent as they are in other solvents. The reactants and reagents for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate adjustments in temperature, pressure and the like, by changing to alternative conventional reagents such as other solvents or other bases, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the method of this invention. In all preparative methods, all starting materials are known or are readily preparable from known starting materials.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

All reagents were used as received except that the bases and solvents were dried as described hereinafter. Unless indicated otherwise, all yields were determined by HPLC according to the following method.

Materials and Methods

Aniline and nitrobenzene were reagent grade and were used without further purification. Solvents were purchased from Aldrich Chemical and were anhydrous grade. The tetramethylammonium hydroxide was purchased as the pentahydrate. The solid was dried in a desiccator over P_2O_5 under vacuum for several days before use. Titration of the resulting solid showed the dried material to be the dihydrate.

HPLC Assay: Reverse phase HPLC was used to analyze the reaction mixtures. A 5 μm Beckman/Altex

Ultrasphere-ODS (4.6×150 mm) column was employed using a ternary gradient pump system.

Elution Gradient				
Time (min)	Flow Rate (mL/Min)	% Water	% ACN	% MeOH
0	1.5	90	10	0
12.0	1.5	63	30	8
12.1	1.5	60	20	20
15	1.5	60	20	20
35	1.5	10	45	45
40	1.5	10	45	45
41	1.5	90	10	0
50	1.5	90	10	0

EXAMPLE 1

A) This example illustrates a neat reaction of aniline and nitrobenzene under aerobic conditions at room temperature to generate 4-NDPA and p-nitrosodiphenylamine (p-NDPA) products. The reaction mixture was then hydrogenated directly to generate 4-ADPA.

A 500 mL three-necked round bottom flask was equipped with a magnetic stir bar. The reaction vessel was charged with 196 mL of aniline and nitrobenzene (4.3 mL, 42 mmole). To the stirred reaction mixture was added tetramethylammonium hydroxide dihydrate (17.7 grams, 140 mmoles) as a solid. The reaction was shown to have consumed nearly all the nitrobenzene after two hours, however, the reaction was allowed to stir for 18 hours. After this time >99% of the nitrobenzene was consumed. HPLC analysis of the reaction mixture indicated the following yields of products based on nitrobenzene: 4-NDPA (6.4 mmole, 1.37 g, 15%). p-NDPA (30.6 mmole, 6.1 g, 73%), 2-NDPA (0.3 mmole, 0.064 g, 0.7%), azobenzene (3.6 mmole, 0.65 g, 8.5%), phenazine (0.8 mmole, 0.14 g, 1.9%). phenazine-N-oxide (0.3 mmole, 0.05 g, 0.7%).

Water (16 ml) was added to the mixture and the entire reaction was then charged into a 300 cc autoclave for hydrogenation. A 1% Pt/carbon catalyst (0.5 grams dry weight) was added to the autoclave. The reaction mixture was heated to 80° C. under 150 psig of H_2. Hydrogen uptake was complete Within 30 minutes. HPLC analysis indicated that 35.9 mmole of 4-ADPA was produced which corresponds to a 97% yield based on moles of 4-NDPA and p-NDPA.

B) This is an example of the reaction of aniline and nitrobenzene at room temperature in dimethylsulfoxide under anaerobic conditions.

A 25 mL round bottom flask was charged with 4 mL of DMSO, aniline, (200 μL, 1.9 mmole) and tetramethylammonium hydroxide dihydrate (330 mg, 2.5 mmole) under argon. The reaction was allowed to proceed at room temperature for 4 hours. Conversion of nitrobenzene was 68%. HPLC analysis indicated the following yields based on nitrobenzene. 4-NDPA (30.5%), p-NDPA (33.6%), azobenzene (2.6%), azoxybenzene (trace).

C) This is an example of a neat reaction between aniline and nitrobenzene at room temperature under anaerobic conditions.

A 25 mL round-bottom flask was charged with aniline (1.8 mL) and nitrobenzene (0.02 mL, 0.19 mmole) in a controlled atmosphere glove box filled with argon. To this solution was added tetramethylammonium hydroxide dihydrate (330 mg, 2.5 mmole). All the nitrobenzene was consumed after several hours. HPLC analysis indicated the following yields based on nitrobenzene: 4-NDPA 10%. p-NDPA 76%, azobenzene 7%, and phenazine 5%.

D) This is an example of the reaction between aniline and nitrobenzene at room temperature in DMSO under aerobic conditions. This example also illustrates generation of 4-NDPA and p-NDPA from its salts utilizing water and acid.

The reaction mixture contained aniline (200 μL, 2.1mmole) and nitrobenzene (200 μL, 1.9 mmole) in 4 mL of DMSO. Tetramethylammonium hydroxide dihydrate (330 mg, 2.5 mmole) was added in one portion. The reaction was allowed to stir for 18 hours after which time 80% of the nitrobenzene had been consumed. The reaction was dumped into 200 mL of water which caused the immediate precipitation of 4-NDPA. The solution was cooled on ice for several hours and the product was filtered off and dried at 100° C. The filtrate was treated with glacial acetic acid until the pH was neutral which caused the precipitation of p-NDPA. The precipitate was filtered and dried at 100° C. Isolated yields based on nitrobenzene consumed: 4-NDPA (66%), p-NDPA (29%).

E) This is an example of the reaction of aniline and nitrobenzene in DMSO at 80° C. under aerobic conditions.

A 250 mL round-bottom flask was charged with aniline (0.05 mole, 4.6 g), nitrobenzene (0.05 mole, 6.1 g) and 75 mL of DMSO. Tetramethylammonium hydroxide dihydrate (0.2 mole, 25.44g) was added to the solution in one portion. The reaction mixture was heated to 80° C. in an oil bath and maintained at that temperature for 5 hours. The reaction was analyzed by HPLC. Yields based on nitrobenzene; 4-NDPA (35%), p-NDPA (51), azobenzene (3.1%).

F) This is an example of the reaction of aniline and nitrobenzene in DMF under aerobic conditions.

Aniline (200 μL, 2.1 mmole) and nitrobenzene (200 μL, 1.9 mmole) was dissolved in 5 mL of DMF. Tetramethylammonium hydroxide dihydrate (1.0 g, 7.8 mmole) was added to the reaction. The reaction was allowed to stir for 2 hours during which time 39% of the nitrobenzene was consumed. Yields based on nitrobenzene consumed: 4-NDPA 99%, p-NDPA trace.

EXAMPLE 2

This example illustrates that the reaction of the present invention can be conducted over a range of temperatures. Four identical reactions were prepared in the following manner and were run at 0°, 23°, 50° and 80° C. in the air. A 50 mL round-bottom flask was charged with 49 mL of aniline and nitrobenzene (1.0 mL, 9.5 mmole). Tetramethylammonium hydroxide dihydrate (4.40 g, 34.6 mmole) was added and the reaction was allowed to proceed for 5 hours. Product yields were determined by HPLC analysis and are based on moles nitrobenzene consumed. Selectivity is the ratio of the moles of product generated and the moles of nitrobenzene consumed. Yield is conversion times selectivity.

TABLE 1

Temp. °C.	Nitrobenzene Conversion	Products	% Selectivity	% Yield
0	52%	p-NDPA	34	18
		4-NDPA	18	9.3
		2-NDPA	2.2	1.0
		phenazine	0.6	0.3
23	73%	p-NDPA	71	51

TABLE 1-continued

Temp. °C.	Nitrobenzene Conversion	Products	% Selectivity	% Yield
		4-NDPA	12	8.5
		azobenzene	17	12
		phenazine		trace
		phenazine-N-oxide		trace
50	98%	p-NDPA	88	86
		4-NDPA	7.8	7.6
		2-NDPA	1.7	1.6
		azobenzene*	22	21
80	100%	p-NDPA	89	89
		4-NDPA	7	7
		2-NDPA	2	2
		azobenzene*	55	55

*The majority of azobenzene is produced presumably through oxidative coupling of aniline. See D. T. Sawyer paper.

EXAMPLE 3

This example illustrates that control of the amount of protic material present in the reaction is important. Four identical reactions were run except the amount of water added to the mixture was varied to include 0, 10, 50, and 100μL. Thus aniline (2 mL) and nitrobenzene (2 mL) were charged into a 25 mL round-bottom flask and various amounts of water were added. Tetramethylammonium hydroxide dihydrate (330 mg, 2.5 mmole) was added in one portion. The reactions were allowed to run in the air at room temperature and were sampled after 16 hours. An identical set of reactions was also run where methanol was added instead of water.

TABLE 2

Volume (μL)	%	Ratio mmole 4-NDPA + p-NDPA/ 2-NDPA + Phenazine	Yield (mmole) 4-NDPA + p-NDPA
Water Added	Water*		
0	2.2	6.2	0.83
10	2.45	8.5	0.68
50	3.45	11.5	0.18
100	4.7	5.0	0.05
Methanol Added	Methanol*		
10	0.25	8.8	0.67
50	1.25	16	0.57
100	2.5	35	0.42

*The % water and methanol is by volume. In the case when no water was added the water present in the reaction was introduced from the tetramethylammonium hydroxide dihydrate.

EXAMPLE 4

This example illustrates that various solvents can be utilized in the practice of the method of this invention to produce 4-NDPA and/or p-NDPA products. The reactions set forth in Table 3 were conducted as in as indicated, except that the solvent of was changed to that indicated in the table.

TABLE 3

Solvent	Reaction Conditions
1-methyl-2-pyrrolidinone	1D
DMSO/THF	1B
pyridine	1D

EXAMPLE 5

This example illustrates various bases which can be utilized in the method of the present invention to produce 4-NDPA and/or p-NDPA products. The reactions set forth in Table 4 were conducted as in Example 1 as indicated except that the base of Example 1 was changed to that indicated in the table.

TABLE 4

Base	Reaction Conditions
Na metal	1D
NaH	1D
NaOH	1D
KOH	1D
Potassium t-butoxide	1D
Lithium bis(trimethylsilyl)amide	1B, 1D
$NaOH/K_2CO_3$	1D, 1F

EXAMPLE 6

This example illustrates the unexpected increase in selectivity and nitrobenzene conversion utilizing the method of the present invention as compared to the method disclosed in Ayyangar et al.

The reaction of acetanilide, nitrobenzene, NaOH, and K_2CO_3 in DMSO was run according to the procedure described by Ayyangar et al. Tetrahedron Letters, Vol. 31, No. 22, pp 3217-3220 (1990). Analysis of this reaction by HPLC indicated 37% of the nitrobenzene was converted and the following yields based on nitrobenzene, were achieved. 4-NDPA (6%), p-NDPA (4.5%), azobenzene (0.7%).

In comparison, when the reaction is conducted according to the teachings of the present invention, the conversions of nitrobenzene and selectivities to the desired products are greatly increased. For example, conducting the reaction as described in Example 1D, aniline (0.05 mole), nitrobenzene (0.05 mole) and tetramethylammonium hydroxide dihydrate (0.2 mole) were mixed in 75 mL of DMSO. The reaction was stirred at room temperature for 5 hours after which time the reaction was analyzed by HPLC chromatography giving the following results. Nitrobenzene conversion was (85%). Yield based on nitrobenzene: 4-NDPA (18%), p-NDPA (51%) azobenzene (3%).

The reaction of acetanilide and nitrobenzene was also run at room temperature. Thus, acetanilide (0.05 mole), nitrobenzene (0.05 mole), NaOH (0.2 mole) and K_2CO_3 were dissolved in 75 mL of DMSO. The reaction was stirred for 5 hours at room temperature (23° C.). Analysis of the reaction showed no conversion of nitrobenzene and no products detected.

EXAMPLE 7

This example illustrates how the ratio of p-NDPA/4-NDPA can be controlled by the ratio of aniline/nitrobenzene.

Aniline and nitrobenzene were reacted at various ratios, while the total reaction volume and the amount of tetramethylammonium hydroxide dihydrate were held constant. Thus, in a typical reaction illustrating an aniline/nitrobenzene volume ratio of 1, aniline (2 mL) and nitrobenzene (2 mL) were charged into a 25 mL round-bottom flask. Tetramethylammonium hydroxide dihydrate (330 mg, 2.5 mmole) was added and the reaction was allowed to proceed at room temperature in air for 14 hours. The reactions were then analyzed by HPLC.

TABLE 5

Volume Ratio Aniline/Nitrobenzene	Ratio p-NDPA/4-NDPA
0.33	0.1

TABLE 5-continued

Volume Ratio Aniline/Nitrobenzene	Ratio p-NDPA/4-NDPA
1	0.1
10	4
50	6

EXAMPLE 8

This example illustrates the effect that the amount of protic material present in or added to the reaction has on the extent of conversion and yields of 4-NDPA and p-NDPA.

The amount of water added to a reaction of aniline, nitrobenzene and tetramethylammonium hydroxide dihydrate in DMSO was varied from zero to 500 μL (0, 50, 150, 300, 500 μL) while keeping the total reaction volume constant. Thus, a typical reaction contained aniline, (200 μL, 2.1 mmole), nitrobenzene (200 μL, 1.9 mmole), tetramethylammonium hydroxide dihydrate (330 mg, 2.5 mmole) and water (50 μL) in 3.55 mL of anhydrous DMSO. The reaction was allowed to react aerobically at room temperature 24 hours after which time it was sampled and subjected to HPLC analysis.

TABLE 6

Volume (μL) Water Added	% Water	% Conversion Nitrobenzene	Yield (mmole) 4-NDPA + p-NDPA
0	2.3	89	150
50	3.5	73	99
150	6	63	62
300	9.75	12	0.23
500	14.7	3	0.05

EXAMPLE 9

This example illustrates the effect that increasing the amount of base has on yields of 4-NDPA and p-NDPA under conditions where the amount of protic material added to the reaction is kept constant.

Three identical reactions were run except that the amount of tetramethylammonium hydroxide dihydrate was varied in each. In a typical reaction, aniline (2 mL), nitrobenzene (2 mL), water (100 μL) and tetramethylammonium hydroxide dihydrate (330 mg, 2.5 mmole) were mixed and allowed to react for 24 hours at room temperature in the air. In those cases where the solution showed large amounts of precipitates, an addition 10 mL of aniline was added to solubilize the reaction before sampling. All of these reactions were analyzed by HPLC.

TABLE 7

Volume Water Added	% Water	Grams Base	mMoles Base	Yield (mmole) 4-NDPA + p-NDPA
100	4.7	0.330	2.5	0.05
100	4.7	0.660	5.0	0.15
100	4.7	1.65	12.5	1.24

EXAMPLE 10

This example illustrates the reaction of aniline, nitrobenzene and tetramethylammonium hydroxide dihydrate under anaerobic conditions at 50° C.

A 500 mL four-necked round-bottom flask equipped with a mechanical stirrer, addition funnel, thermometer, and nitrogen inlet was charged with 90 mL of aniline. The aniline was purged with nitrogen and tetramethylammonium hydroxide dihydrate (54 g, 0.42 mole) was added in one portion. The reaction mixture was heated to 50° C. under a nitrogen blanket with stirring. Once the temperature in the reaction vessel reached 50° C., nitrobenzene (10 mL, 95 mmole) was added dropwise to the vigorously stirred mixture of aniline and base. The nitrobenzene was added at a rate such that the addition was complete within 30 minutes. The temperature of the reaction increased to 65° C. during the nitrobenzene addition. The reaction was allowed to stir for an additional 90 minutes after which time it was analyzed by HPLC. Nitrobenzene conversion = 100%. Yields based on nitrobenzene: p-NDPA (88.5%), 4-NDPA (4.3%), phenazine (3.6%), azobenzene (3.6%).

EXAMPLE 11

This example illustrates that tetramethylammonium ion salt of 4-NDPA and p-NDPA can be produced in the method of the present invention.

Aniline (3.0 mL) was stirred with tetramethylammonium hydroxide dihydrate (330 mg, 2.5 mmole) in a controlled atmosphere dry box under argon. The aniline base mixture was filtered such that the aniline was delivered directly to 1 mL of nitrobenzene. Upon addition of the aniline-base solution, the reaction immediately turned red and a precipitate began to form. The mixture was allowed to stir for 5 minutes after which time the reaction was filtered. The red precipitate was washed with several volumes of dry ether and allowed to dry. A portion of the solid was analyzed by ^{1}H-NMR spectroscopy: (DMSO) δ 3.1(s), 6.1 (d, 1), 6.5 (t, 1), 6.6 (d,1), 6.76 (d, 1), 6.8 (t, 1), 7.04 (t, 1) 7.5 (d,1). A drop of acetic acid-d_4 was added to the NMR tube which caused an immediate color change from red to yellow and the sample was re-subjected to ^{1}H-NMR spectroscopy. The resulting spectrum was identical to authentic 4-NDPA. A portion of the red solid was dissolved in wet acetonitrile and subjected to HPLC analysis which indicated that 4-NDPA was the major component.

EXAMPLE 12

This example illustrates the conversion of 4-ADPA to N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine, a useful antiozonant for the protection of rubber products.

52 grams of 4-ADPA, prepared by the reaction of aniline and nitrobenzene (by the procedure of Example 1D), 100 grams methylisobutylketone (MIBK) and 0.3 grams of 3% platinum on carbon catalyst were charged into a one liter Parr autoclave. After purging with hydrogen, the reaction mixture was heated to 170°-175° C. and 800 psig hydrogen applied. The mixture was reacted for 95 minutes and a sample withdrawn. GC analysis indicated 0.4% unreacted 4-ADPA present. The reaction mixture was cooled and filtered to remove catalyst and stripped to remove water and excess MIBK. The product, 71 grams, on cooling crystallized to a purplish solid. Assay by GC internal standard method indicated 95.9% purity.

Similar reactions were conducted with similar results using methylisoamylketone and acetone.

The preceding examples can be repeated with similar success by substituting the generically or specifically described solvents, bases and the like and/or operating conditions, such as other temperatures and pressures, of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this

invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A method of producing one or more 4-ADPA intermediates comprising the steps of:
   a) bringing aniline and nitrobenzene into reactive contact in a suitable solvent system; and
   b) reacting the aniline and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and a controlled amount of protic material to produce one or more 4-ADPA intermediates.

2. Method of claim 1 wherein said suitable solvent system includes a solvent selected from aniline, nitrobenzene, dimethylsulfoxide, dimethylformamide, pyridine and mixtures thereof.

3. Method of claim 2 wherein said solvent is selected from aniline, dimethylsulfoxide, and dimethylformamide.

4. Method of claim 2 wherein said solvent is aniline.

5. Method of claim 2 wherein said solvent is nitrobenzene.

6. Method of claim 2 wherein said solvent is dimethylsulfoxide.

7. Method of claim 2 wherein said solvent is dimethylformamide.

8. Method of claim 2 wherein said solvent is N-methylpyrolidone.

9. Method of claim 2 wherein said solvent is pyridine.

10. Method of claim 2 wherein said suitable solvent system includes a protic solvent.

11. Method of claim 10 wherein said protic solvent is selected from methanol, water and mixtures thereof.

12. Method of claim 1 wherein said solvent system includes aniline and up to about 4 v/v % water based on the total volume of the reaction mixture.

13. Method of claim 1 wherein said solvent system includes dimethylsulfoxide and up to about 8 v/v % water based on the total volume of the reaction mixture.

14. Method of claim 1 wherein said solvent system includes aniline and up to about 3 v/v % methanol based on the total volume of the reaction mixture.

15. Method of claim 1 wherein said suitable temperature is from about −10° C. to about 150° C.

16. Method of claim 1 wherein said suitable base is selected from organic and inorganic bases.

17. The method of claim 16 wherein said organic and inorganic bases include alkali metals, alkali metal hydrides, alkali metal hydroxides, alkali metal alkoxides, phase transfer catalysts in conjunction with a base source, aminos and mixtures thereof.

18. The method of claim 1 wherein said base is an alkali metal.

19. The method of claim 1 wherein said base is an alkali metal hydride.

20. The method of claim 1 wherein said base is an alkali metal hydroxide.

21. The method of claim 1 wherein said base is a phase transfer catalyst in conjunction with a base source.

22. The method of claim 1 wherein said base is selected from an aryl, alkyl, and aryl/alkyl ammonium salt in conjunction with a base source.

23. The method of claim 1 wherein said base is a crown ether.

24. The method of claim 1 wherein said base is an amine.

25. The method of claim 1 wherein said base is combined with aniline to form a mixture, which mixture is then brought into reactive contact with nitrobenzene.

26. The method of claim 1 wherein said aniline and nitrobenzene are combined to form a mixture to which the base is added.

27. The method of claim 1 wherein said solvent is aniline and said base is a tetraalkylammonium hydroxide.

28. The method of claim 1 wherein said aniline and nitrobenzene are reacted under aerobic conditions.

29. The method of claim 1 wherein said aniline and nitrobenzene are reacted under anaerobic conditions.

30. A method of producing 4-aminodiphenylamine (4-ADPA) comprising the steps of:
   a) bringing aniline and nitrobenzene into reactive contact in a suitable solvent system;
   b) reacting the aniline and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and controlled amount of protic material to produce one or more 4-ADPA intermediates; and
   c) reducing the 4-ADPA intermediates under conditions which produce 4-ADPA.

31. Method of claim 30 wherein said suitable solvent system includes a solvent selected from aniline, nitrobenzene, dimethylsulfoxide, dimethylformamide, N-methylpyrolidone, pyridine and mixtures thereof.

32. Method of claim 31 wherein said solvent is selected from aniline, dimethylsulfoxide, dimethylformamide, and mixtures thereof.

33. Method of claim 31 wherein said solvent is aniline.

34. Method of claim 31 wherein said solvent is nitrobenzene.

35. Method of claim 31 wherein said solvent is dimethylsulfoxide.

36. Method of claim 31 wherein said solvent is dimethylformamide.

37. Method of claim 31 wherein said solvent is N-methylpyrolidone.

38. Method of claim 31 wherein said solvent is pyridine.

39. Method of claim 31 wherein said suitable solvent system includes a protic solvent.

40. Method of claim 39 wherein said protic solvent is selected from methanol, water and mixtures thereof.

41. Method of claim 30 wherein said solvent system includes aniline and up to about 4 v/v % water based on the total volume of the reaction mixture.

42. Method of claim 30 wherein said solvent system includes dimethylsulfoxide and up to about 8 v/v % water based on the volume of the reaction mixture.

43. Method of claim 30 wherein said solvent system includes aniline and up to about 3 v/v % methanol based on the volume of the reaction mixture.

44. Method of claim 30 wherein said suitable temperature is from about −10° C. to about 150° C.

45. Method of claim 30 wherein said suitable base is selected from organic and inorganic bases.

46. The method of claim 45 wherein said organic and inorganic bases include alkali metals, alkali metal hydrides, alkali metal hydroxides, phase transfer catalysts in conjunction with a base source, and mixtures thereof.

47. The method of claim 30 wherein said base is an alkali metal.

48. The method of claim 30 wherein said base is an alkali metal hydride.

49. The method of claim 30 wherein said base is an alkali metal hydroxide.

50. The method of claim 30 wherein said base is a phase transfer catalyst in conjunction with a base source.

51. The method of claim 30 wherein said base is selected from an aryl, alkyl and aryl/alkyl ammonium salt in conjunction with a base source.

52. The method of claim 30 wherein said base is a crown ether in conjunction with a base source.

53. The method of claim 30 wherein said base is an amine.

54. The method of claim 30 wherein said base is combined with aniline to form a mixture, which mixture is then brought into reactive contact with nitrobenzene.

55. The method of claim 30 wherein said aniline and nitrobenzene are combined to form a mixture to which the base is added.

56. The method of claim 30 wherein said solvent is aniline and said base is a tetraalkylammonium hydroxide.

57. The method of claim 30 wherein said aniline and nitrobenzene are reacted under aerobic conditions.

58. The method of claim 30 wherein said aniline and nitrobenzene are reacted under anaerobic conditions.

59. A method of claim 30 wherein said 4-ADPA intermediates are reduced utilizing hydrogen in the presence of a suitable catalyst.

60. A method of claim 59 wherein said catalyst is platinum on carbon.

61. A method of producing alkylated p-phenylenediamines comprising the steps of:

a) bringing aniline and nitrobenzene into reactive contact in a suitable solvent system;

b) reacting the aniline and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and controlled amount of protic material to produce one or more 4-ADPA intermediates.

c) reducing the 4-ADPA intermediates to produce 4-ADPA; and

d) reductively alkylating the 4-ADPA of Step c).

62. Method of claim 61 wherein said suitable solvent system includes a solvent selected from aniline, nitrobenzene, dimethylsulfoxide, dimethylformamide, pyridine and mixtures thereof.

63. Method of claim 62 wherein said solvent is selected from aniline, dimethylsulfoxide, dimethylformamide, and mixtures thereof.

64. Method of claim 62 wherein said solvent is aniline.

65. Method of claim 62 wherein said solvent is nitrobenzene.

66. Method of claim 62 wherein said solvent is dimethylsulfoxide.

67. Method of claim 62 wherein said solvent is dimethylformamide.

68. Method of claim 62 wherein said solvent is N-methylpyrolidone.

69. Method of claim 62 wherein said solvent is pyridine.

70. Method of claim 62 wherein said suitable solvent system includes a protic solvent.

71. Method of claim 70 wherein said protic solvent is selected from methanol, water and mixtures thereof.

72. Method of claim 62 wherein said solvent system includes aniline and up to about 4 v/v % water based on the volume of the reaction mixture.

73. Method of claim 62 wherein said solvent system includes dimethylsulfoxide and up to about 8 v/v % water based on the volume of the reaction mixture.

74. Method of claim 62 wherein said solvent system includes aniline and up to about 3 v/v % methanol based on the volume of the reaction mixture.

75. Method of claim 62 wherein said suitable temperature is from about −10° C. to about 150° C.

76. Method of claim 62 wherein said suitable base is selected from organic and inorganic bases.

77. The method of claim 76 wherein said organic and inorganic bases include alkali metals, alkali metal hydrides, alkali metal hydroxides, alkali metal alkoxides, phase transfer catalysts in conjunction with a base source, amines and mixtures thereof.

78. The method of claim 62 wherein said base is an alkali metal.

79. The method of claim 62 wherein said base is an alkali metal hydride.

80. The method of claim 62 wherein said base is an alkali metal hydroxide.

81. The method of claim 62 wherein said base is a phase transfer catalyst in conjunction with a base source.

82. The method of claim 62 wherein said base is selected from an aryl, alkyl, and aryl/alkyl ammonium salt in conjunction with a base source.

83. The method of claim 62 wherein said base is a crown ether.

84. The method of claim 62 wherein said base is an amine.

85. The method of claim 62 wherein said base is combined with aniline to form a mixture, which mixture is then brought into reactive contact with nitrobenzene.

86. The method of claim 62 wherein said aniline and nitrobenzene are combined to form a mixture to which the base is added.

87. The method of claim 62 wherein said solvent is aniline and said base is a tetraalkylammonium hydroxide.

88. The method of claim 62 wherein said aniline and nitrobenzene are reacted under aerobic conditions.

89. The method of claim 62 wherein said aniline and nitrobenzene are reacted under anaerobic conditions.

90. The method of claim 61 Wherein said 4-ADPA is reductively alkylated utilizing a ketone selected from the group consisting of acetone, methylisobutylketone, methylisoamylketone, and 2-octanone.

91. Method of claim 90 wherein said ketone is acetone.

92. Method of claim 90 wherein said ketone is methylisobutylketone.

93. Method of claim 90 wherein said ketone is methylisoamylketone.

94. Method of claim 90 wherein said ketone is 2-octanone.

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U.S. PATENT: *5,608,111*
ISSUE DATE: *March 04, 1997*

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United States Patent [19]

Stern et al.

[11] Patent Number: 5,608,111

[45] Date of Patent: *Mar. 4, 1997

[54] **METHOD OF PREPARING 4-AMINODIPHENYLAMINE**

[75] Inventors: **Michael K. Stern**, University City; **James M. Allman**; **James K. Bashkin**, both of St. Louis, all of Mo.; **Roger K. Rains**, Richfield, Ohio

[73] Assignee: **Flexsys America L. P.**, Akron, Ohio

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,117,063.

[21] Appl. No.: **435,607**

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Related U.S. Application Data

[63] Continuation of Ser. No. 157,120, filed as PCT/US92/02232, Mar. 27, 1992, Pat. No. 5,453,541, which is a continuation-in-part of Ser. No. 719,876, Jun. 21, 1991, Pat. No. 5,117,063.

[51] **Int. Cl.**[6] **C07C 209/02**; C07C 209/26; C07C 209/36; C07C 209/38

[52] **U.S. Cl.** **564/398**; 564/397; 564/408; 564/420; 564/421; 564/422; 564/423; 564/433; 564/434

[58] **Field of Search** 564/397, 398, 564/408, 420, 421, 422, 423, 433, 434

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Primary Examiner—Richard L. Raymond

Attorney, Agent, or Firm—G. B. Seward; Kenneth D. Goetz

[57] **ABSTRACT**

A method of producing 4-ADPA is disclosed wherein aniline or substituted aniline derivatives and nitrobenzene are reacted under suitable conditions to produce 4-nitrodiphenylamine or substituted derivatives thereof and/or 4-nitrosodiphenylamine or substituted derivatives thereof and/or their salts, either or both of which are subsequently reduced to produce 4-ADPA or substituted derivatives thereof. The 4-ADPA or substituted derivatives thereof can be reductively alkylated to produce p-phenylenediamine products or substituted derivatives thereof which are useful as antiozonants. A second embodiment of the invention is the tetrasubstituted ammonium salts or alkyl substituted diammonium salts of 4-nitrodiphenylamine, 4-nitrosodiphenylamine and the substituted derivatives thereof wherein each substituent of the tetrasubstituted ammonium ion is independently selected from the group consisting of alkyl, aryl and arylalkyl groups and each alkyl substituent of the alkyl substituted diammonium salt is independently selected.

31 Claims, No Drawings

METHOD OF PREPARING 4-AMINODIPHENYLAMINE

This application is a Continuation of U.S. Ser. No. 08/157,120 filed Dec. 6, 1993, now U.S. Pat. No. 5,453,541 which is a 35 USC 371 of PCT/US92/02232 filed Mar. 27, 1992, which is a Continuation-in-part of U.S. Ser. No. 07/719,876 filed Jun. 21, 1991, now U.S. Pat. No. 5,117,063 issued May 26, 1992.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to methods for preparing 4-aminodiphenylamine (4-ADPA) and, more particularly, relates to a method for preparing 4-ADPA wherein aniline is reacted with nitrobenzene in the presence of a base, and under conditions wherein the amount of protic material, e.g., water, is controlled, to produce a mixture rich in the salt of 4-nitrodiphenylamine and/or the salt of 4-nitrosodiphenylamine. The 4-nitrodiphenylamine and/or 4-nitrosodiphenylamine salts can be isolated and subsequently hydrogenated or, alternatively, the reaction mixture itself is hydrogenated, to produce 4-ADPA in high yield. The present invention also relates to methods for preparing 4-ADPA intermediates as well as to alkylated p-phenylenediamine products useful as antioxidants.

2. Related Art

It is known to prepare 4-ADPA by way of a nucleophilic aromatic substitution mechanism, wherein an aniline derivative replaces halide. This method involves preparation of a 4-ADPA intermediate, namely 4-nitrodiphenylamine (4-NDPA) followed by reduction of the nitro moiety. The 4-NDPA is prepared by reacting p-chloronitrobenzene with an aniline derivative, such as formanilide or an alkali metal salt thereof, in the presence of an acid acceptor or neutralizing agent, such as potassium carbonate, and, optionally, utilizing a catalyst. See, for example, U.S. Pat. Nos. 4,187,248; 4,683,332; 4,155,936; 4,670,595; 4,122,118; 4,614,817; 4,209,463; 4,196,146; 4,187,249; 4,140,716. This method is disadvantageous in that the halide that is displaced is corrosive to the reactors and appears in the waste stream and must therefore be disposed of at considerable expense. Furthermore, use of an aniline derivative such as formanilide, and use of p-chloro-nitrobenzene, requires additional manufacturing equipment and capabilities to produce such starting materials from aniline and nitrobenzene, respectively.

It is also known to prepare 4-ADPA from the head-to-tail coupling of aniline. See, for example, G.B. 1,440,767 and U.S. Pat. No. 4,760,186. This method is disadvantageous in that the yield of 4-ADPA is not acceptable for a commercial process. It is also known to decarboxylate a urethane to produce 4-NDPA. See U.S. Pat. No. 3,847,990. However, such method is not commercially practical in terms of cost and yield.

It is known to prepare 4-ADPA by hydrogenating p-nitrosodiphenylhydroxylamine which can be prepared by catalytic dimerization of nitrosobenzene utilizing, as a reducing agent, aliphatic compounds, benzene, naphthalene or ethylenically unsaturated compounds. See, for example, U.S. Pat. Nos. 4,178,315 and 4,404,401. It is also known to prepare p-nitrosodiphenylamine from diphenylamine and an alkyl nitrate in the presence of excess hydrogen chloride. See, for example, U.S. Pat. Nos. 4,518,803 and 4,479,008.

It is also known to produce 4-nitrosodiphenylamine by reacting acetanilide and nitrobenzene in DMSO in the presence of sodium hydroxide and potassium carbonate at 80° C. for 5 hours. See Ayyangar et al., Tetrahedron Letters, Vol. 31, No. 22, pp. 3217–3220 (1990). See also, Wohl, Chemische Berichte, 36, p. 4135 (1903) and Chemische Berichte, 34, p. 2442 (1901). However, the yield of 4-nitrosodiphenylamine is low and is therefore not commercially practical. Furthermore, such method requires utilization of an aniline derivative, namely, acetanilide, and therefore increases the cost of the starting materials.

The process of the present invention does not include a halide source and therefore eliminates the expensive halide removal from the waste stream. In addition, the process of the present invention is much less expensive in terms of manufacturing costs, as well as the cost of raw materials, because instead of the derivatives of aniline and nitrobenzene, the present method utilizes aniline and nitrobenzene directly.

SUMMARY OF THE INVENTION

The present invention is directed to a method of preparing 4-ADPA intermediates or the substituted derivatives thereof, e.g., 4-nitrodiphenylamine (4-NDPA) and the salts thereof, and/or 4-nitrosodiphenylamine (p-NDPA or 4-NODPA) and/or the salts thereof, wherein aniline or substituted aniline derivatives and nitrobenzene are brought into reactive contact in a suitable solvent system, and then reacted in the presence of a base and under conditions wherein the amount of protic material, such as water, is controlled. The resulting reaction mixture is rich in 4-ADPA intermediates or the substituted derivatives thereof, including the 4-nitrodiphenylamine and/or 4-nitrosodiphenylamine salts. The process can be utilized according to the teachings of the present invention to produce a high yield of the 4-nitroso product (p-nitrosodiphenylamine and its salt) with little or no 4nitro product. The 4-nitroso reaction product mixture can then be hydrogenated directly, or the 4-nitroso product can then be isolated and subsequently hydrogenated, to produce 4-ADPA in high yield. Similarly, the 4-nitro product (4-nitrodiphenylamine and its salt) can be produced in high yield with little or no 4-nitroso product, and the 4-nitro product, or the isolated 4-nitro product, can be hydrogenated to produce 4-ADPA in high yield. Alternatively, the 4-nitro and 4-nitroso products are both produced and are not isolated but the reaction mixture is hydrogenated directly to produce 4-ADPA. The resulting 4-ADPA can be utilized to prepare alkylated products of p-phenylenediamine, which products are useful as antioxidants and antiozonants. Alternatively, the 4-ADPA intermediates can be reduced and the reduced material alkylated in the same reaction vessel utilizing a ketone as a solvent.

In one embodiment of the invention, the amount of protic material present during the reaction of aniline or substituted aniline derivatives and nitrobenzene is controlled by having a desiccant present during the reaction. In another embodiment, the amount of protic material present during the reaction of aniline or substituted aniline derivatives and nitrobenzene is controlled by continuously removing protic material by distillation.

The present invention is further directed to the tetrasubstituted ammonium salts or alkyl substituted diammonium salts of 4-nitrodiphenylamine, 4-nitrosodiphenylamine and the substituted derivatives thereof wherein each substituent of the tetrasubstituted ammonium salt is independently

selected from the group consisting of alkyl, aryl and arylalkyl groups and each alkyl substituent of the alkyl substituted diammonium salt is independently selected.

DETAILED DESCRIPTION OF THE INVENTION

The subject method for producing 4-ADPA intermediates involves the steps of:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system;

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone, such as a reactor, at a suitable temperature and in the presence of a suitable base and a controlled amount of protic material, such as water, to produce 4-nitrodiphenylamine or substituted derivatives thereof and its salt and/or 4-nitfosodiphenylamine or substituted derivatives thereof and its salt.

For producing 4-ADPA or substituted derivatives thereof, the subject method includes the following step:

c) reducing the 4-nitrosodiphenylamine or substituted derivatives thereof and its salt and/or the 4-nitrodiphenylamine or substituted derivatives thereof and its salt to produce 4-ADPA.

For producing alkylated p-phenylenediamines or substituted derivatives thereof, the subject method includes the step of:

d) reductively alkylating the 4-ADPA or substituted derivatives thereof of Step c).

As utilized herein, the term "4-ADPA intermediates" means 4-nitrodiphenylamine, 4-nitrosodiphenylamine (also referred to as p-nitrosodiphenylamine), the substituted derivatives thereof and the salts thereof. Thus, reference to "one or more 4-ADPA intermediates" refers to one or both of the neutral compounds, i.e., those that are not in the form of a salt, and/or the salt of one or both of such compounds. The salt is produced in the reaction mixture from reaction of the 4-nitro and/or 4-nitroso products with the base. Thus, the reaction mixture produced in the method of the present invention can include one of the compounds or salts or any combination thereof depending on the specific reaction conditions selected.

The molar ratio of aniline or substituted aniline derivatives to nitrobenzene can vary from a large excess of nitrobenzene to a large excess of aniline or substituted aniline derivative. Preferably, the reaction is conducted utilizing an excess of aniline or substituted aniline derivative. The ratio of 4-nitro to 4-nitroso produced in the reaction of the present invention can be controlled by varying the ratio of aniline to nitrobenzene. For example, the higher the ratio of aniline to nitrobenzene, the higher the ratio of 4-nitroso to 4-nitro. Conversely, the higher the ratio of nitrobenzene to aniline, the higher the ratio of 4-nitro to 4-nitroso.

As used herein, the term "substituted aniline derivatives" means aniline containing one or more electron withdrawing or electron releasing substituents on the aromatic ring. Applicable substituents include, but are not limited to, halides, $—NO_2$, $—NH_2$, alkyl groups, alkoxy groups, $—SO_3$, —COOH and aryl, aralkyl or alkaryl groups containing at least one $—NH_2$ group. Halides are selected from the group consisting of chloride, bromide and fluoride. The preferred alkyl and alkoxy groups contain from 1 to about 6 carbon atoms. The preferred aryl, aralkyl and alkaryl groups contain from about 6 to about 18 carbon atoms. Examples of substituted aniline derivatives include, but are not limited to, 2-methoxyaniline, 4-methoxyaniline, 4-chloroaniline, p-toluidine, 4-nitroaniline, 3-bromoaniline, 3-bromo-4-aminotoluene, p-aminobenzoic acid, 2,4-diaminotoluene, 2,5-dichloroaniline, 1,4-phenylene diamine, 4,4'-methylene dianiline, 1,3,5-triaminobenzene and mixtures thereof.

Aniline or substituted aniline derivatives can be added directly or can be formed in situ by addition of a compound that will form aniline or the corresponding aniline derivative under the conditions present in the reaction system.

Azobenzene is also produced in this reaction in variable quantities depending on the reaction conditions. One way of controlling azobenzene production is through the ratio of aniline to nitrobenzene. Thus, as this ratio is increased, the amount of azobenzene generally decreases. As discussed below, and as illustrated in the Examples set forth below, other variables, such as the amount of base and oxygen, can also affect the amount of azobenzene produced. Thus, utilizing the teachings of the present invention, one skilled in the art can conduct the reaction of the present invention to control the amount of azobenzene that is produced.

Suitable solvent systems include, but are not limited to, solvents such as, for example, dimethylsulfoxide, N-methylpyrrolidone, dimethylformamide, aniline, pyridine, nitrobenzene, nonpolar hydrocarbon solvents such as toluene and hexane, ethyleneglycol dimethyl ether, diisopropyl ethylamine, and the like, as well as mixtures thereof. Preferably, aniline or substituted aniline derivative is used in excess in the reaction as stated above, and the aniline or substituted aniline derivative in excess of the molar amount of nitrobenzene serves as the solvent. As described in more detail below, solvent mixtures can be utilized wherein one or more of the suitable solvents and another solvent, such as a controlled amount of a protic solvent, e.g., methanol, are combined.

Suitable bases include, but are not limited to, organic and inorganic bases such as, for example, alkali metals, such as sodium metal, alkali metal hydrides, hydroxides and alkoxides, such as sodium hydride, lithium hydroxide, sodium hydroxide, cesium hydroxide, potassium hydroxide, potassium t-butoxide, and the like, including mixtures thereof. Other acceptable base materials include, but are not limited to, phase transfer catalysts in conjunction with a suitable base source such as tetrasubstituted ammonium hydroxides wherein each substituent is independently selected from alkyl, aryl or arylalkyl groups wherein the alkyl, aryl and arylalkyl groups preferably have 1 to about 18 carbon atoms, including tetraalkylammonium hydroxides, e.g., tetramethylammonium hydroxide, aryl, trialkyl ammonium hydroxides, e.g., phenyltrimethylammonium hydroxide, arylalkyl, trialkylammonium hydroxides, e.g., benzyl trimethylammonium hydroxide, alkyl substituted diammonium hydroxides, e.g., bis-dibutylethyl hexamethylene diammonium hydroxide, and other combinations of phase transfer catalysts and suitable bases such as suitable bases in conjunction with aryl ammonium salts, crown ethers and the like, and amine bases, such as lithium bis(trimethylsilyl) amide, and the like, including mixtures thereof. Preferred materials (bases) for use as bases are tetraalkylammonium hydroxides such as tetramethylammonium hydroxide. Preferably, the base is added to the aniline or substituted aniline derivative to produce a mixture which is then combined with the nitrobenzene. Alternatively, the base can be added after the aniline or substituted aniline derivative and nitrobenzene have been combined. Addition of materials can be above or below surface addition. The amount of base utilized in the

present process can vary over a wide range. For example, the reaction can be conducted in a manner which is limiting in base or the reaction can be conducted in a manner which is limiting in nitrobenzene or aniline or substituted aniline derivative depending, among other factors, on the desired degree of minimization of azobenzene.

The reaction is conducted at a suitable temperature which can vary over a wide range. For example, the temperature can fall within a range of from about −10° C. to about 150° C., such as from about 0° C. to about 100° C., preferably from about 10° C. to about 90° C. A most preferred temperature for conducting the reaction of the present invention is from about 60° C. to about 80° C., such as at 75° C. Where aniline is utilized as the solvent under aerobic reaction conditions, as the temperature of the reaction increases, the amount of azobenzene produced increases. However, where the reaction is conducted in aniline under anaerobic conditions, higher temperatures do not necessarily increase the amount of azobenzene. Where production of azobenzene is not a problem, higher temperatures will be suitable. However, where it is desired to minimize the amount of azobenzene, lower temperatures or anaerobic reaction conditions are more suitable. Alternatively, to minimize the amount of azobenzene while conducting the reaction at higher temperatures, a solvent other than aniline can be used and the ratio of aniline or substituted aniline derivative to nitrobenzene can be controlled.

Control of the amount of protic material present in the reaction is important. Generally, when the reaction is conducted in aniline, water present in the reaction in an amount greater than about 4% H_2O, (based on volume of the reaction mixture) inhibits the reaction of the aniline with the nitrobenzene to an extent where the reaction is no longer significance. Reducing the amount of water to below the 4% level causes the reaction to proceed in an acceptable manner. When tetramethylammonium hydroxide is utilized as a base with aniline as the solvent, as the amount of water is reduced further, e.g., down to about 0.5% based on the volume of the reaction mixture, the total amount of 4-nitrodiphenylamine and 4-nitrosodiphenylamine and/or salts thereof increases with some loss in selectivity so that more 2-nitrodiphenylamine is produced but still in minor amounts. Thus, the present reaction could be conducted under anhydrous conditions. A "controlled amount" of protic material is an amount up to that which inhibits the reaction of aniline with nitrobenzene, e.g., up to about 4% H_2O based on the volume of the reaction mixture when aniline is utilized as the solvent. The upper limit for the amount of protic material present in the reaction varies with the solvent. For example, when DMSO is utilized as the solvent and tetramethylammonium hydroxide is utilized as the base, the upper limit on the amount of protic material present in the reaction is about 8% H_2O based on the volume of the reaction mixture. When aniline is utilized as a solvent with the same base, the upper limit is 4% H_2O based on the volume of the reaction mixture. In addition, the amount of protic material tolerated will vary with type of base, amount of base, and base cation, used in the various solvent systems. However, it is within the skill of one in the art, utilizing the teachings of the present invention, to determine the specific upper limit of the amount of protic material for a specific solvent, type and amount of base, base cation and the like. The minimum amount of protic material necessary to maintain selectivity of the desired products will also depend on the solvent, type and amount of base, base cation and the like, that is utilized and can also be determined by one skilled in the art.

Since the amount of protic material present in the reaction is important, it is possible to reduce the amount of protic material present as much as possible and then add back to the reaction the desired amount, e.g., 0.5 vol. % when aniline is used as the solvent. Protic materials that can be utilized to add back to the reaction are known to those skilled in the art and include, but are not limited to, water, methanol and the like. Methods for measuring the amount of protic material and for reducing the amount of protic material as much as possible are well known in the art. For example, the amount of water present in certain reagents can be determined by utilizing a Karl-Fischer apparatus, and the amount of water can be reduced through distillation and/or drying under reduced pressure, drying in the presence of P_2O_5 and other agents, azeotropic distillation utilizing, for example, aniline, and the like, including combinations thereof.

In one embodiment for controlling the amount of protic material during the reaction of aniline or substituted aniline derivatives and nitrobenzene, a desiccant is added so as to be present during the reaction of aniline or substituted aniline derivative and nitrobenzene. For example, when the protic material is water, the desiccant removes water present during the reaction of aniline or substituted aniline derivatives and nitrobenzene and results in higher conversion of nitrobenzene and yields of 4-nitrodiphenylamine and 4-nitrosodiphenylamine or substituted derivatives thereof. As used herein, desiccant is a compound present during the reaction of aniline or substituted aniline derivatives and nitrobenzene in addition to the suitable base used. Examples of suitable desiccants include, but are not limited to, anhydrous sodium sulfate, molecular sieves such as types 4A, 5A and 13X available from the Union Carbide Corporation, calcium chloride, tetramethyl ammonium hydroxide dihydrate, anhydrous bases such as KOH and NaOH, and activated alumina.

In another embodiment for controlling the amount of protic material during the reaction of aniline or substituted aniline derivatives and nitrobenzene, protic material is continuously removed from the reaction mixture by distillation. When the protic material is water, the preferred method involves continuous azeotropic distillation of water utilizing the water/aniline azeotrope. The continuous distillation of protic material is the currently preferred method for controlling the amount of protic material present during the reaction of aniline or substituted aniline derivatives and nitrobenzene. The continuous removal of protic material allows the use of lower amounts of base in the reaction of aniline or substituted aniline derivatives and nitrobenzene while achieving very high conversion of nitrobenzene and excellent yields of 4-nitrodiphenylamine and 4-nitrosodiphenylamine and/or salts thereof or substituted derivatives thereof.

The reaction can be conducted under aerobic or anaerobic conditions. Under aerobic conditions, the reaction is conducted essentially as described above in a reaction zone which is exposed to oxygen, usually by exposure to air. Under aerobic conditions, the pressure at which the reaction is conducted can vary and the optimal pressure, as well as the optimal combination of pressure and temperature/pressure conditions, are easily determined by one skilled in the art. For example, the reaction can be conducted at room temperature and at a pressure ranging from about 10 psig to about 250 psig, such as from about 14 to about 150 psig. Under anaerobic conditions, the reaction can be conducted at atmospheric pressure or reduced or increased pressures, in the presence of a neutral gas such as, for example, nitrogen or argon. Optimal conditions for a particular set of reaction parameters, such as temperature, base, solvent and the like, are easily determined by one skilled in the art utilizing the

teachings of the present invention. It has been observed that less azobenzene is produced when the reaction is conducted anaerobically with aniline as the solvent. It has also been observed that less azobenzene is produced when the reaction is conducted aerobically with DMSO, and other similar solvents, as the solvent.

The 4-nitrodiphenylamine or substituted derivatives thereof and/or 4-nitrosodiphenylamine or substituted derivatives thereof and/or their salts can be reduced to 4-ADPA or substituted derivatives thereof. The neutral compounds can be generated from the salts utilizing water and/or an acid. See, for example, Example 1D. Alternatively, the salts can be reduced as shown in Example 1A. This reduction can be carried out by any of many known reductive processes, such as using a hydride source, e.g., sodium borohydride in conjunction with palladium- or platinum-on-carbon catalyst. Preferably, this reduction is conducted by a catalytic reduction wherein hydrogenation is effected under hydrogen pressure in the presence of platinum- or palladium-on-carbon, nickel, and the like. This hydrogenation process is described in detail in "Catalytic Hydrogenation in Organic Synthesis", P. N. Rylander, Academic Press, N.Y., p. 299 (1979), which is hereby incorporated herein by reference. The hydrogenation can be conducted in a variety of solvents including, but not limited to, toluene, xylene, aniline, 4-ADPA, water and mixtures thereof. Preferably, the hydrogenation is conducted utilizing a platinum-on-carbon or palladium-on-carbon catalyst in a suitable solvent such as, for example, either toluene, 4-ADPA, xylene or aniline, mixtures thereof, or mixtures which include water as the solvent and a hydrogen pressure of from 100 psig H_2 to about 340 psig H_2 at a temperature of about 80° C.

Reductive alkylation of 4-ADPA to produce antiozonants can be conducted by any one of several well known methods. See, for example, U.S. Pat. No. 4,900,868. Preferably, 4-ADPA and a suitable ketone or aldehyde are reacted in the presence of hydrogen and platinum on carbon as catalyst. Suitable ketones include methylisobutyl ketone (MIBK), acetone, methylisoamylketone and 2-octanone. It should be noted that reduction of the 4-ADPA intermediates and alkylation of the reduced material can be conducted in the same reaction vessel utilizing the ketone as a solvent. See, for example, U.S. Pat. No. 4,463,191, and Banerjee et al, J. Chem. Soc. Chem. Comm. 18, 1275–76 (1988).

Contemplated equivalents of the reactants and reagents set forth above are reactants and reagents otherwise corresponding thereto and having the same general properties wherein one or more of the various groups, e.g., NO_2, are simple variations. In addition, where a substituent is designated as, or can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position is not critical so long as it does not adversely affect the overall activity and/or synthesis procedure.

The chemical reactions described above are generally disclosed in terms of their broadest application to the method of this invention. Occasionally, the reaction conditions may not be applicable as specifically described to each reactant and reagent within the disclosed scope. For example, certain suitable bases may not be as soluble in one solvent as they are in other solvents. The reactants and reagents for which this occurs will be readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate adjustments in temperature, pressure and the like, by changing to alternative conventional reagents such as other solvents or other bases, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the method of this invention. In all preparative methods, all starting materials are known or are readily preparable from known starting materials.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

All reagents were used as received except that the bases and solvents were dried as described hereinafter. Unless indicated otherwise, all yields were determined by HPLC according to the following method.

Materials and Methods Aniline or substituted aniline derivatives and nitrobenzene were reagent grade and were used without further purification. Solvents were purchased from Aldrich Chemical and were anhydrous grade. The tetramethylammonium hydroxide was purchased as the pentahydrate. The solid was dried in a desiccator over P_2O_5 under vacuum for several days before use. Titration of the resulting solid showed the dried material to be the dihydrate.

HPLC Assay: Reverse phase HPLC was used to analyze the reaction mixtures. A 5 μm Beckman/Altex Ultrasphere-ODS (4.6×150 mm) column was employed using a ternary gradient pump system.

	Elution Gradient			
Time (min)	Flow Rate (mL/Min)	% Water	% ACN	% MeOH
0	1.5	90	10	0
12.0	1.5	63	30	8
12.1	1.5	60	20	20
15	1.5	60	20	20
35	1.5	10	45	45
40	1.5	10	45	45
41	1.5	90	10	0
50	1.5	90	10	0

EXAMPLE 1

A) This example illustrates a neat reaction of aniline and nitrobenzene under aerobic conditions at room temperature to generate 4-NDPA and p-nitrosodiphenylamine (p-NDPA) products. The reaction mixture was then hydrogenated directly to generate 4-ADPA.

A 500 mL three-necked round bottom flask was equipped with a magnetic stir bar. The reaction vessel was charged with 196 mL of aniline and nitrobenzene (4.3 mL, 42 mmole). To the stirred reaction mixture was added tetramethylammonium hydroxide dihydrate (17.7 grams, 140 mmoles) as a solid. The reaction was shown to have consumed nearly all the nitrobenzene after two hours, however, the reaction was allowed to stir for 18 hours. After this time >99% of the nitrobenzene was consumed. HPLC analysis of the reaction mixture indicated the following yields of products based on nitrobenzene: 4-NDPA (6.4 mmole, 1.37 g, 15%). p-NDPA (30.6 mmole, 6.1 g, 73%), 2-NDPA (0.3 mmole, 0.064 g, 0.7%), azobenzene (3.6 mmole, 0.65 g, 8.5%), phenazine (0.8 mmole, 0.14 g, 1.9%). phenazine-N-oxide (0.3 mmole, 0.05 g, 0.7%).

Water (16 ml) was added to the mixture and the entire reaction was then charged into a 300 cc autoclave for hydrogenation. A 1% Pt/carbon catalyst (0.5 grams dry weight) was added to the autoclave. The reaction mixture was heated to 80° C. under 150 psig of H_2. Hydrogen uptake was complete within 30 minutes. HPLC analysis indicated that 35.9 mmole of 4-ADPA was produced which corresponds to a 97% yield based on moles of 4-NDPA and p-NDPA.

B) This is an example of the reaction of aniline and nitrobenzene at room temperature in dimethylsulfoxide under anaerobic conditions.

A 25 mL round bottom flask was charged with 4 mL of DMSO, aniline, (200 μL, 1.9 mmole) and tetramethylammonium hydroxide dihydrate (330 mg, 2.5 mmole) under argon. The reaction was allowed to proceed at room temperature for 4 hours. Conversion of nitrobenzene was 68%. HPLC analysis indicated the following yields based on nitrobenzene. 4-NDPA (30.5%), p-NDPA (33.6%), azobenzene (2.6%), azoxybenzene (trace).

C) This is an example of a neat reaction between aniline and nitrobenzene at room temperature under anaerobic conditions.

A 25 mL round-bottom flask was charged with aniline (1.8 mL) and nitrobenzene (0.02 mL, 0.19 mmole) in a controlled atmosphere glove box filled with argon. To this solution was added tetramethylammonium hydroxide dihydrate (330 mg, 2.5 mmole). All the nitrobenzene was consumed after several hours. HPLC analysis indicated the following yields based on nitrobenzene: 4-NDPA 10%. p-NDPA 76%, azobenzene 7%, and phenazine 5%.

D) This is an example of the reaction between aniline and nitrobenzene at room temperature in DMSO under aerobic conditions. This example also illustrates generation of 4-NDPA and p-NDPA from its salts utilizing water and acid.

The reaction mixture contained aniline (200 μL, 2.1 mmole) and nitrobenzene (200 μL, 1.9 mmole) in 4 mL of DMSO. Tetramethylammonium hydroxide dihydrate (330 mg, 2.5 mmole) was added in one portion. The reaction was allowed to stir for 18 hours after which time 80% of the nitrobenzene had been consumed. The reaction was dumped into 200 mL of water which caused the immediate precipitation of 4-NDPA. The solution was cooled on ice for several hours and the product was filtered off and dried at 100° C. The filtrate was treated with glacial acetic acid until the pH was neutral which caused the precipitation of p-NDPA. The precipitate was filtered and dried at 100° C. Isolated yields based on nitrobenzene consumed: 4-NDPA (66%), p-NDPA (29%).

E) This is an example of the reaction of aniline and nitrobenzene in DMSO at 80° C. under aerobic conditions.

A 250 mL round-bottom flask was charged with aniline (0.05 mole, 4.6 g), nitrobenzene (0.05 mole, 6.1 g) and 75 mL of DMSO. Tetramethylammonium hydroxide dihydrate (0.2 mole, 25.44 g) was added to the solution in one portion. The reaction mixture was heated to 80° C. in an oil bath and maintained at that temperature for 5 hours. The reaction was analyzed by HPLC. Yields based on nitrobenzene; 4-NDPA (35%), p-NDPA (51%), azobenzene (3.1%).

F) This is an example of the reaction of aniline and nitrobenzene in DMF under aerobic conditions.

Aniline (200 μL, 2.1 mmole) and nitrobenzene (200 μL, 1.9 mmole) was dissolved in 5 mL of DMF. Tetramethylammonium hydroxide dihydrate (1.0 g, 7.8 mmole) was added to the reaction. The reaction was allowed to stir for 2 hours during which time 39% of the nitrobenzene was consumed. Yields based on nitrobenzene consumed: 4-NDPA 99%, p-NDPA trace.

EXAMPLE 2

This example illustrates that the reaction of the present invention can be conducted over a range of temperatures. Four identical reactions were prepared in the following manner and were run at 0°, 23°, 50° and 80° C. in the air. A 50 mL round-bottom flask was charged with mL of aniline and nitrobenzene (1.0 mL, 9.5 mmole). Tetramethylammonium hydroxide dihydrate (4.40 g, 34.6 mmole) was added and the reaction was allowed to proceed for 5 hours. Product yields were determined by HPLC analysis and are based on moles nitrobenzene consumed. Selectivity is the ratio of the moles of product generated and the moles of nitrobenzene consumed. Yield is conversion times selectivity.

TABLE 1

Temp. °C.	Nitrobenzene Conversion	Products	% Selectivity	% Yield
0	52%	p-NDPA	34	18
		4-NDPA	18	9.3
		2-NDPA	2.2	1.0
		phenazine	0.6	0.3
23	73%	p-NDPA	71	51
		4-NDPA	12	8.5
		azobenzene	17	12
		phenazine		trace
		phenazine-N-oxide		trace
50	98%	p-NDPA	88	86
		4-NDPA	7.8	7.6
		2-NDPA	1.7	1.6
		azobenzene*	22	21
80	100%	p-NDPA	89	89
		4-NDPA	7	7
		2-NDPA	2	2
		azobenzene*	55	55

*The majority of azobenzene is produced presumably through oxidative coupling of aniline. See D. T. Sawyer paper.

EXAMPLE 3

This example illustrates that control of the amount of protic material present in the reaction is important. Four identical reactions were run except the amount of water added to the mixture was varied to include 0, 10, 50, and 100 μL. Thus aniline (2 mL) and amount of water added to the mixture was varied to include 1, 10, 50, and 100 μL. Thus aniline (2 mL) and nitrobenzene (2 mL) were charged into a 25 mL round-bottom flask and various amounts of water were added. Tetramethylammonium hydroxide dihydrate (330 mg, 2.5 mmole) was added in one portion. The reactions were allowed to run in the air at room temperature and were sampled after 16 hours. An identical set of reactions was also run where methanol was added instead of water.

TABLE 2

Volume (μL) Water Added	% Water*	Ratio mmole 4-NDPA + p-NDPA/ 2-NDPA + Phenazine	Yield (mmole) 4-NDPA + p-NDPA
0	2.2	6.2	0.83
10	2.45	8.5	0.68
50	3.45	11.5	0.18
100	4.7	5.0	0.05
Volume (μL) Methanol Added	**% Methanol***		
10	0.25	8.8	0.67
50	1.25	16	0.57
100	2.5	35	0.42

*The % water and methanol is by volume. In the case when no water was added the water present in the reaction was introduced from the tetramethylammonium hydroxide dihydrate.

EXAMPLE 4

This example illustrates that various solvents can be utilized in the practice of the method of this invention to

produce 4-NDPA and/or p-NDPA products. The reactions set forth in Table 3 were conducted as in Example 1 as indicated, except that the solvent of Example 1 was changed to that indicated in the table.

TABLE 3

Solvent	Reaction Conditions
N-methyl-2-pyrrolidone	1D
DMSO/THF	1B
pyridine	1D

EXAMPLE 5

This example illustrates various bases which can be utilized in the method of the present invention to produce 4-NDPA and/or p-NDPA products. The reactions set forth in Table 4 were conducted as in Example 1 as indicated except that the base of Example 1 was changed to that indicated in the table.

TABLE 4

Base	Reaction conditions
Na metal	1D
NaH	1D
NaOH	1D
KOH	1D
Potassium t-butoxide	1D
Lithium bis(trimethylsilyl)amide	1B, 1D
$NaOH/K_2CO_3$	1D, 1F

EXAMPLE 6

This example illustrates the unexpected increase in selectivity and nitrobenzene conversion utilizing the method of the present invention as compared to the method disclosed in Ayyangar et al.

The reaction of acetanilide, nitrobenzene, NaOH, and K_2CO_3 in DMSO was run according to the procedure described by Ayyangar et al. Tetrahedron Letters, Vol. 31, No. 22, pp 3217–3220 (1990). Analysis of this reaction by HPLC indicated 37% of the nitrobenzene was converted and the following yields based on nitrobenzene, were achieved. 4-NDPA (6%), pNDPA (4.5%), azobenzene (0.7%).

In comparison, when the reaction is conducted according to the teachings of the present invention, the conversions of nitrobenzene and selectivities to the desired products are greatly increased. For example, conducting the reaction as described in Example 1D, aniline (0.05 mole), nitrobenzene (0.05 mole) and tetramethylammonium hydroxide dihydrate (0.2 mole) were mixed in 75 mL of DMSO. The reaction was stirred at room temperature for 5 hours after which time the reaction was analyzed by HPLC chromatography giving the following results. Nitrobenzene conversion was (85%). Yield based on nitrobenzene: 4-NDPA (18%), p-NDPA (51%) azobenzene (3%).

The reaction of acetanilide and nitrobenzene was also run at room temperature. Thus, acetanilide (0.05 mole), nitrobenzene (0.05 mole), NaOH (0.2 mole) and K_2CO_3 were dissolved in 75 mL of DMSO. The reaction was stirred for 5 hours at room temperature (23° C.). Analysis of the reaction showed no conversion of nitrobenzene and no products detected.

EXAMPLE 7

This example illustrates how the ratio of p-NDPA/4-NDPA can be controlled by the ratio of aniline/nitrobenzene.

Aniline and nitrobenzene were reacted at various ratios, while the total reaction volume and the amount of tetramethylammonium hydroxide dihydrate were held constant. Thus, in a typical reaction illustrating an aniline/nitrobenzene volume ratio of 1, aniline (2 mL) and nitrobenzene (2 mL) were charged into a 25 mL round-bottom flask. Tetramethylammonium hydroxide dihydrate (330 mg, 2.5 mmole) was added and the reaction was allowed to proceed at room temperature in air for 14 hours. The reactions were then analyzed by HPLC.

TABLE 5

Volume Ratio Aniline/Nitrobenzene	Ratio p-NDPA/4-NDPA
0.33	0.1
1	0.1
10	4
50	6

EXAMPLE 8

This example illustrates the effect that the amount of protic material present in or added to the reaction has on the extent of conversion and yields of 4-NDPA and p-NDPA.

The amount of water added to a reaction of aniline, nitrobenzene and tetramethylammonium hydroxide dihydrate in DMSO was varied from zero to 500 μL (0, 50, 150, 300, 500 μL) while keeping the total reaction volume constant. Thus, a typical reaction contained aniline, (200 μL, 2.1 mmole), nitrobenzene (200 μL, 1.9 mmole), tetramethylammonium hydroxide dihydrate (330 mg, 2.5 mmole) and water (50 μL) in 3.55 mL of anhydrous DMSO. The reaction was allowed to react aerobically at room temperature 24 hours after which time it was sampled and subjected to HPLC analysis.

TABLE 6

Volume (μL) Water Added	% Water	% Conversion Nitrobenzene	Yield (mmole) 4-NDPA + p-NDPA
0	2.3	89	1.5
50	3.5	73	0.99
150	6	63	0.62
300	9.75	12	0.23
500	14.7	3	0.05

EXAMPLE 9

This example illustrates the effect that increasing the amount of base has on yields of 4-NDPA and p-NDPA under conditions where the amount of protic material added to the reaction is kept constant.

Three identical reactions were run except that the amount of tetramethylammonium hydroxide dihydrate was varied in each. In a typical reaction, aniline (2 mL), nitrobenzene (2 mL), water (100 μL) and tetramethylammonium hydroxide dihydrate (330 mg, 2.5 mmole) were mixed and allowed to react for 24 hours at room temperature in the air. In those cases where the solution showed large amounts of precipitates, an additional 10 mL of aniline was added to solubilize the reaction before sampling. All of these reactions were analyzed by HPLC.

TABLE 7

Volume Water Added	% Water	Grams Base	mMoles Base	Yield (mmole) 4-NDPA + p-NDPA
100	4.3	0.330	2.5	0.05
100	5.9	0.660	5.0	0.15
100	9.6	1.65	12.5	1.24

EXAMPLE 10

This example illustrates the reaction of aniline, nitrobenzene and tetramethylammonium hydroxide dihydrate under anaerobic conditions at 50° C.

A 500 mL four-necked round-bottom flask equipped with a mechanical stirrer, addition funnel, thermometer, and nitrogen inlet was charged with 90 mL of aniline. The aniline was purged with nitrogen and tetramethylammonium hydroxide dihydrate (54 g, 0.42 mole) was added in one portion. The reaction mixture was heated to 50° C. under a nitrogen blanket with stirring. Once the temperature in the reaction vessel reached 50° C., nitrobenzene (10 mL, 95 mmole) was added dropwise to the vigorously stirred mixture of aniline and base. The nitrobenzene was added at a rate such that the addition was complete within 30 minutes. The temperature of the reaction increased to 65° C. during the nitrobenzene addition. The reaction was allowed to stir for an additional 90 minutes after which time it was analyzed by HPLC. Nitrobenzene conversion=100%. Yields based on nitrobenzene: p-NDPA (88.5%), 4-NDPA (4.3%), phenazine (3.6%), azobenzene (3.6%).

EXAMPLE 11

This example illustrates that tetramethylammonium ion salt of 4-NDPA and p-NDPA can be produced in the method of the present invention.

Aniline (3.0 mL) was stirred with tetramethylammonium hydroxide dihydrate (330 mg, 2.5 mmole) in a controlled atmosphere dry box under argon. The aniline base mixture was filtered such that the aniline was delivered directly to 1 mL of nitrobenzene. Upon addition of the aniline-base solution, the reaction immediately turned red and a precipitate began to form. The mixture was allowed to stir for 5 minutes after which time the reaction was filtered. The red precipitate was washed with several volumes of dry ether and allowed to dry. A portion of the solid was analyzed by ^{1}H-NMR spectroscopy: (DMSO) δ3.1(s), 6.1 (d, 1), 6.5 (t, 1), 6.6 (d,1), 6.76 (d, 1), 6.8 (t, 1), 7.04 (t, 1) 7.5 (d, 1). A drop of acetic acid-d_4 was added to the NMR tube which caused an immediate color change from red to yellow and the sample was re-subjected to ^{1}H-NMR spectroscopy. The resulting spectrum was identical to authentic 4-NDPA. A portion of the red solid was dissolved in wet acetonitrile and subjected to HPLC analysis which indicated that 4-NDPA was the major component.

EXAMPLE 12

This example illustrates the conversion of 4-ADPA to N-(1,3-dimethylbutyl)-N'-phenyl-p-phenylenediamine, a useful antiozonant for the protection of rubber products.

52 grams of 4-ADPA, prepared by the reaction of aniline and nitrobenzene (by the procedure of Example 1D), 100 grams methylisobutylketone (MIBK) and 0.3 grams of 3% platinum on carbon catalyst were charged into a one liter Parr autoclave. After purging with hydrogen, the reaction mixture was heated to 170°–175° C. and 800 psig hydrogen applied. The mixture was reacted for 95 minutes and a sample withdrawn. GC analysis indicated 0.4% unreacted 4-ADPA present. The reaction mixture was cooled and filtered to remove catalyst and stripped to remove water and excess MIBK. The product, 71 grams, on cooling crystallized to a purplish solid. Assay by GC internal standard method indicated 95.9% purity.

Similar reactions were conducted with similar results using methylisoamylketone and acetone.

The following examples utilized an improved HPLC analysis method. The external standard method was used for the analysis of the coupling reaction products by HPLC. A Waters 600 series HPLC equipped with a Vydac 201HS54 (4.6×250 mm) column and UV detection at 254 nm was used to monitor all reactions

	Elution Gradient	
Time (min)	% Solvent A (Water)	% Solvent B (40% Methanol in ACN)
0	75	25
35	20	80
40	0	100
45	0	100
46	75	25
55	75	25

External standards were prepared by dissolving N-methyl aniline (5.7 mg), nitrobenzene (13.0 mg), phenazine (4.5 mg), 4-nitrosodiphenylamine (68.1 mg), 4-nitrodiphenylamine (7.2 mg), azobenzene (4.7 mg) and 25% aqueous solution of tetramethylammoniumhydroxide (130 μL) in 50 mL of acetonitrile. In the cases where aniline derivatives are used similar standard solutions were generated.

EXAMPLE 13

This example illustrates the continuous removal of water from the reaction of aniline, nitrobenzene and tetramethylammonium hydroxide (TMA(H)) by a vacuum distillation of the aniline/water azeotrope.

A 22 liter round bottom flask equipped with mechanical stirrer, Dean—Stark condenser, thermocouple, nitrobenzene addition line, and teflon baffle was charged with 15.1 lbs. of a 25% aqueous TMA(H) solution (6.70 L, 18.8 Moles TMA(H)). Water was removed by vacuum distillation (55 torr) to the point where the base concentration was 35%. During this step the reaction temperature rose steadily to a value between 50°–55° C. Aniline (22.2 lbs, 9.88 L, 108 Mole) was charged into the reactor and the vacuum distillation was continued at 55 torr. Water and aniline were steadily removed as the azeotrope until the molar ratio of water to TMA(H) was 4:1. During this process the temperature of the reaction increased to 75° C. Once the appropriate molar ratio of water to base was achieved, nitrobenzene (4.83 lbs., 1.79 L, 17.82 Mole) was added continuously over a period of three hours. During this addition water and aniline are continuously being removed from the reaction by vacuum distillation at 55 torr. A good rate of water/aniline removal is to have the weight of the condensate removed equal the weight of nitrobenzene added over the entire addition time. The reaction endpoint can be determined by HPLC analysis by monitoring the conversion of nitrobenzene. Typical yields determined by HPLC analysis at 100% conversion of nitrobenzene: 4-nitrosodiphenylamine 92.1%,

4-nitrodiphenylamine 3.4%, azobenzene 3.4%, and phenazine 0.9%.

EXAMPLE 14

This example illustrates the use of various solvents in the reaction of aniline, nitrobenzene and base to generate 4-ADPA intermediates.

To a solution containing 0.5 g (5.3 mmole) of aniline and 0.95 g (6.5 mmole) of tetramethylammonium hydroxide dihydrate in 8 ml of solvent at 70° C. under nitrogen, 0.65 g (5.3 mmole) of nitrobenzene was added via a syringe. After the solution was stirred at 70° C. under nitrogen for 12 hours the reaction was analyzed by HPLC with the results summarized in Table 8.

TABLE 8

Solvent	Nitrobenzene Conversion	Yield Phenazine	Yield 4-NODPA	Yield 4-NDPA	Yield Azobenzene
Toluene	99.5	0.64	76.4	20.9	1.5
Hexane	94.8	1.1	36.0	34.1	23.5
Ethylene glycol dimethyl ether	100	1.24	51.4	27	19.8
Diisopropyl ethyl amine	50	0.9	45	4.3	0

EXAMPLE 15

This example illustrates how a variety of different phase transfer catalysts can be employed in the reaction of aniline, nitrobenzene and base to produce 4-ADPA intermediates.

In a typical reaction a three necked round bottom flask equipped with Dean—Stark condenser was charged with 59 g (0.091 mole base) of aqueous tetrabutylammonium hydroxide and 55 g (0.59 mole) of aniline. Water was removed via azeotropic distillation with aniline 35 ml at 20 mmHg at 70° C. Nitrobenzene 11.2 g (0.091 mole) was introduced via a dropping funnel at 70° C. over 5 minutes. The reaction was stirred at 20 mmHg/70° C. for 4 hours. The reaction was analyzed by HPLC with the results summarized in Table 9.

In the case where bis-dibutylethyl hexamethylenediamine ammonium hydroxide was used as base the reaction conditions were slightly different. Thus 50 mL of the aqueous quaternary ammonium hydroxide solution (0.0575 mmole hydroxide) was mixed with 200 mL of aniline. The water was removed by vacuum distillation at 67° C. until 28 mL of water had been distilled. Nitrobenzene (23.2 mmole, 2.85 g) was added dropwise to the reaction under a nitrogen atmosphere at 50° C. The reaction was allowed to stir for 2 hours after which time a sample was withdrawn for analysis.

TABLE 9

Base	Nitrobenzene Conversion	Yield % Phenazine	Yield % 4-NODPA	Yield % 4-NDPA	Yield % Azobenzene
Tetrabutyl ammonium hydroxide	77.5%	0	52.1	9.7	3.4
Tetrapropyl ammonium hydroxide	100%	0.25	63.8	18.3	17.5
Choline hydroxide	83.6%	0.85	33.0	9.6	43.2
Benzyltrimethyl ammonium hydroxide	100%	0.1	74.7	12.4	11.7
18-crown-6 + 2KOH	99.4%	0.33	77.8	11.5	6.54
Bis-dibutylethyl hexamethylene diammonium hydroxide	85.3%	0	76	7	1.1

EXAMPLE 16

This example illustrates how the addition of an external desiccant can be used to absorb water in this reaction in replacement of the azeotropic distillation described in Example 13.

A 500 mL three necked round bottom flask equipped with mechanical stirrer and Dean-Stark condenser was charged with 59.01 grams (0.162 Mole base) of 25% aqueous tetramethylammonium hydroxide solution. Water (17 mL) was removed under vacuum distillation at 20 torr. Aniline (88.05 grams) was added and 18 mL of water was removed under vacuum which results in a water to base molar ratio of 3:1. The distillation was stopped and an appropriate desiccant was added. Nitrobenzene (19.18 grams, 0.155 mole) was then added over one hour under a nitrogen blanket. During the addition the reaction temperature was maintained at 70° C. The reaction was allowed to continue for one hour after the addition of nitrobenzene was complete. The results of these experiments are summarized in Table 10.

TABLE 10

Desiccant	Grams Added	Nitrobenzene Conversion	Yield % Phenazine	Yield % 4-NODPA	Yield % 4-NDPA	Yield % Azobenzene
None	—	52.3%	0.34	46.7	2.0	1.0
Anhydrous Sodium Sulfate	14.75	61.9%	0.50	58.6	2.2	0.8

TABLE 10-continued

Desiccant	Grams Added	Nitrobenzene Conversion	Yield % Phenazine	4-NODPA	4-NDPA	Azobenzene
4Å Molecular Sieves	28.1	78.2%	1.0	68.0	5.1	4.8

EXAMPLE 17

This example illustrates how the amount of phenazine produced in this reaction can be reduced by increasing the steric bulk of the tetraalkylammonium ion used as phase transfer catalyst. The experimental procedure used is identical to that described in Example 15. The results are summarized in Table 11.

TABLE 11

Base	Nitrobenzene Conversion	Yield % Phenazine	4-NODPA	4-NDPA	Azobenzene
Tetramethyl ammonium hydroxide	100%	2.24	43	34	12.1
Tetrapropyl ammonium hydroxide	100%	0.25	63.8	18.3	17.5
Benzyltrimethyl ammonium hydroxide	100%	0.1	74.7	12.4	11.7
Tetrabutyl ammonium hydroxide	77.5%	0	52.1	9.7	3.4
Phenyltrimethyl ammonium hydroxide	48%	22	15	12	23

EXAMPLE 18

This example illustrates how various substituted aniline derivatives can be employed in this reaction. The reactions were analyzed by HPLC and the results are summarized in Table 12.

A) 3-Bromoaniline:

A solution of 10 ml (0.09 mole) of 3-bromoaniline and 1.5 g (0.01 mole) of tetramethylammonium hydroxide dihydrate was stirred at 70 C under nitrogen. Nitrobenzene 0.9 ml (8.78 mmole) was added dropwise via a syringe and the solution was stirred at 70° C. under nitrogen for 12 hours.

B) 4-Nitroaniline:

A solution of (1.38 g, 0.01 mole) of 4-nitroaniline and 1.81 g (0.012 mole) of tetramethylammonium hydroxide dihydrate in 3 ml of dimethylsulfoxide was stirred at 70° C. under nitrogen. Nitrobenzene 1 ml (0.01 mole) was added dropwise via a syringe and the solution was stirred at 70° C. under nitrogen for 12 hours.

C) p-Toluidine:

A solution of (3 g, 28 mmole) of p-toluidine and 0.9 g (6 mmole) of tetramethylammonium hydroxide dihydrate was stirred at 70° C. under nitrogen. Nitrobenzene 0.5 ml (5 mmole) was added dropwise via a syringe and the solution was stirred at 70° C. under nitrogen for 12 hours.

D) 4-Chloroaniline:

A solution of (4.8 g, 0.03 mole) of -chloroaniline and 0.9 g (6 mmole) of tetramethylammonium hydroxide dihydrate in 2 ml of dimethylsulfoxide was stirred at 70° C. under nitrogen. Nitrobenzene 0.71 g (5.6 mmole) was added dropwise via a syringe and the solution was stirred at 70° C. under nitrogen for 12 hours.

E) 4-Methoxyaniline:

A solution of 3 g (0.03 mole) of 4-methoxyaniline and 0.95 g (6 mmole) of tetramethylammonium hydroxide dihydrate in 2 ml of dimethylsulfoxide was stirred at 70° C. under nitrogen. Nitrobenzene (0.6 g, 5 mmole) was added dropwise via a syringe and the solution was stirred at 70° C. under nitrogen for 12 hours.

F) 2-Methoxyaniline:

A solution of (4.9 g, 0.03 mole) of 2-methoxyaniline and 1.1 g (7.58 mmole) of tetramethylammonium hydroxide dihydrate was stirred at 70° C. under nitrogen. Nitrobenzene 0.75 g (6.09 mmole) was added dropwise via a syringe and the solution was stirred at 70° C. under nitrogen for 12 hours.

TABLE 12

Aniline Derivative	Nitrobenzene Conversion	Yield % 4-NODPA Derivative	4-NDPA Derivative
2-Methoxyaniline	100	55	44
4-Methoxyaniline	100	74	20
4-Chloroaniline	98	61	8
p-Toluidine	100	19	9
4-Nitroaniline	99	0	73
3-Bromoaniline	100	61	9

EXAMPLE 19

This example illustrates how a variety of diamino nucleophiles will couple to the para position of nitrobenzene.

Nitrobenzene (2 ml, 0.02 mole) was added via a syringe to a stirring solution containing 1.08 g (0.01 mole) of 1,4-phenylenediamine, 3.6 g (0.02 mole) of tetramethylammonium hydroxide pentahydrate in 2 ml of dimethylsulfoxide under nitrogen at 70° C. The solution was stirred at such condition for 4 hours. An aliquot was taken out for LC, MS, LC-MS analyses. N,N'-(4-nitrosophenyl)-1,4-phenylenediamine, N-(4-nitrophenyl)-N'-(4-nitrosophenyl)-1,4-phenylenediamine and N,N'-(4-nitrophenyl)-1,4-phenylenediamine were obtained.

Other diamino nucleophiles such as 4,4'-methylenedianiline and 2,4-diaminotoluene also give similar results under identical reaction conditions.

EXAMPLE 20

This example illustrates the hydrogenation of 4-NODPA/tetramethyl ammonium (TMA) salt and 4-NDPA/TMA salt to 4-ADPA in various solvents. The hydrogenation reactions were carried out in a 300 cc stainless steel autoclave equipped with mechanical stirrer and temperature control.

A) 4-NODPA/TMA salt (12.4 grams, 0.0464 mmole) was charged into the autoclave with 150 mL of toluene. A 1% Pt/Carbon catalyst (300 mg dry weight) was added to the autoclave. The reactor was purged with nitrogen and then was placed under 200 psig hydrogen which was maintained constant throughout the hydrogenation. The reactions were stirred at 1500 rpm and were allowed to attain a temperature of 80° C. Upon the termination of hydrogen uptake the reaction was assumed to be complete. The material was removed and filtered to remove catalyst. The organic layer was sampled and assayed by reverse phase HPLC which revealed 100% conversion of substrate and 97% yield of 4-ADPA.

B) A mixture of 4-NODPA/TMA salt (71 g, 262 mmole) and 4-NDPA/TMA salt (7 g, 24 mmole) was charged into the autoclave with 150 grams of aniline. A 1% Pt/carbon catalyst was added (300 mg dry weight). The reactor was purged with nitrogen and then was placed under 200 psig hydrogen which was maintained constant throughout the reaction. The reactions were stirred at 1500 rpm and were allowed to attain a temperature of 80° C. Upon the termination of hydrogen uptake the reaction was assumed to be complete. The material was removed and filtered to remove catalyst. The organic layer was sampled and assayed by reverse phase HPLC which revealed 100% conversion of substrate and 98% yield of 4-ADPA.

C) A mixture of 4-NODPA/TMA salt (36.5 g, 135 mmole) and 4-NDPA/TMA salt (3.4 g. 12 mmole) was charged into the autoclave with 51 grams of 4-ADPA. A 1% Pt/carbon catalyst (300 mg dry weight) was added. The reactor was purged with nitrogen and then was placed under 200 psig hydrogen which was maintained constant throughout the reaction. The reactions were stirred at 1500 rpm and were allowed to attain a temperature of 80% C. Upon the termination of hydrogen uptake the reaction was assumed to be complete. The material was removed and filtered to remove catalyst. The organic layer was sampled and assayed by reverse phase HPLC which revealed 100% conversion of substrate and with 4-ADPA being the only major product detected.

EXAMPLE 21

This example illustrates the hydrogenation of 4-NODPA to 4-ADPA in aniline using a supported nickel catalyst.

Fifty grams of 4-NODPA, 200 grams aniline and 2.0 grams nickel on silica-alumina support was charged into a one liter autoclave. After purging to exclude oxygen, the mixture was heated to 80° C. and hydrogen feed initiated at 200 mL/min. The feed was limited so that the maximum pressure was 280 psig. After 120 minutes the hydrogen flow indicated that the reaction was complete. A sample was withdrawn and analysis indicated 0.1% unreacted 4-NODPA remained. The product was 4-ADPA.

The preceding examples can be repeated with similar success by substituting the generically or specifically described solvents, bases and the like and/or operating conditions, such as other temperatures and pressures, of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A method of producing one or more 4-ADPA intermediates comprising:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system; and

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and a controlled amount of protic material to produce one or more 4-ADPA intermediates wherein a desiccant is present during step (b) to control the amount of protic material present during the reaction of aniline or substituted aniline derivative and nitrobenzene.

2. The method of claim 1 wherein said desiccant is selected from the group consisting of anhydrous sodium sulfate, molecular sieves, calcium chloride, tetramethyl ammonium hydroxide dihydrate, anhydrous potassium hydroxide, anhydrous sodium hydroxide and activated alumina.

3. A method of producing one or more 4-ADPA intermediates comprising:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system; and

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and a controlled amount of protic material to produce one or more 4-ADPA intermediates wherein the amount of protic material in step (b) is controlled by the continuous distillation of said protic material.

4. The method of claim 3 wherein said protic material is water and said water is removed by continuous azeotropic distillation utilizing the water/aniline azeotrope.

5. A method of producing 4-aminodiphenylamine (4-ADPA) or substituted derivatives thereof comprising:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system;

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and controlled amount of protic material to produce one or more 4-ADPA intermediates: and

c) reducing the 4-ADPA intermediates under conditions which produce 4-ADPA or substituted derivatives thereof wherein a desiccant is present during step (b) to control the amount of protic material present during the reaction of aniline or substituted aniline derivative and nitrobenzene.

6. The method of claim 5 wherein said desiccant is selected from the group consisting of anhydrous sodium sulfate, molecular sieves, calcium chloride, tetramethyl ammonium hydroxide dihydrate, anhydrous potassium hydroxide, anhydrous sodium hydroxide and activated alumina.

7. A method of producing 4-aminodiphenylamine (4-ADPA) or substituted derivatives thereof comprising:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system;

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and controlled amount of protic material to produce one or more 4-ADPA intermediates; and

c) reducing the 4-ADPA intermediates under conditions which produce 4-ADPA or substituted derivatives thereof wherein the amount of protic material in step (b) is controlled by the continuous distillation of said protic material.

8. The method of claim **7** wherein said protic material is water and said water is removed by continuous azeotropic distillation utilizing the water/aniline azeotrope.

9. A method of producing alkylated p-phenylenediamines or substituted derivatives thereof comprising:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system;

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and controlled amount of protic material to produce one or more 4-ADPA intermediates;

c) reducing the 4-ADPA intermediates to produce 4-ADPA or substituted derivatives thereof; and

d) reductively alkylating the 4-ADPA or substituted derivatives thereof of step (c) wherein a desiccant is present during step (b) to control the amount of protic material present during the reaction of aniline or substituted aniline derivative and nitrobenzene.

10. The method of claim **9** wherein said desiccant is selected from the group consisting of anhydrous sodium sulfate, molecular sieves, calcium chloride, tetramethyl ammonium hydroxide dihydrate, anhydrous potassium hydroxide, anhydrous sodium hydroxide and activated alumina.

11. A method of producing alkylated p-phenylenediamines or substituted derivatives thereof comprising:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system;

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and controlled amount of protic material to produce one or more 4-ADPA intermediates;

c) reducing the 4-ADPA intermediates to produce 4-ADPA or substituted derivatives thereof; and

d) reductively alkylating the 4-ADPA or substituted derivatives thereof of step (c) wherein the amount of protic material in step (b) is controlled by the continuous distillation of said protic material.

12. The method of claim **11** wherein said protic material is water and said water is removed by continuous azeotropic distillation utilizing the water/aniline azeotrope.

13. The method of claim **1** wherein said suitable base is selected from the group consisting of tetrasubstituted ammonium hydroxides, alkyl substituted diammonium hydroxides and mixtures thereof, wherein each substituent of said tetrasubstituted ammonium hydroxide is independently selected from alkyl, aryl or arylalkyl groups.

14. The method of claim **13** wherein said suitable base is a tetrasubstituted ammonium hydroxide.

15. The method of claim **14** wherein said tetrasubstituted ammonium hydroxide is a tetraalkyl ammonium hydroxide.

16. The method of claim **15** wherein said tetraalkyl ammonium hydroxide is tetramethyl ammonium hydroxide.

17. The method of claim **13** wherein said suitable solvent is aniline.

18. The method of claim **3** wherein said suitable base is selected from the group consisting of tetrasubstituted ammonium hydroxides, alkyl substituted diammonium hydroxides and mixtures thereof, wherein each substituent of said tetrasubstituted ammonium hydroxide is independently selected from alkyl, aryl or arylalkyl groups.

19. The method of claim **18** wherein said suitable base is a tetrasubstituted ammonium hydroxide.

20. The method of claim **19** wherein said tetrasubstituted ammonium hydroxide is a tetraalkyl ammonium hydroxide.

21. The method of claim **20** wherein said tetraalkyl ammonium hydroxide is tetramethyl ammonium hydroxide.

22. The method of claim **18** wherein said suitable solvent is aniline.

23. A method of producing one or more 4-ADPA intermediates comprising:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system,

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and protic material to produce one or more 4-ADPA intermediates, and

c) controlling the amount of said protic material in step (a) or (b) to provide a selectivity of at least 0.97, wherein the selectivity is the molar ratio of 4-ADPA intermediates to undesired products.

24. The method of claim **23** wherein said suitable base is selected from the group consisting of tetrasubstituted ammonium hydroxides, alkyl substituted diammonium hydroxides and mixtures thereof, wherein each substituent of said tetrasubstituted ammonium hydroxide is independently selected from alkyl, aryl or arylalkyl groups.

25. The method of claim **24** wherein said suitable base is a tetra-substituted ammonium hydroxide.

26. The method of claim **25** wherein said tetrasubstituted ammonium hydroxide is a tetraalkyl ammonium hydroxide.

27. The method of claim **26** wherein said tetraalkyl ammonium hydroxide is tetramethyl ammonium hydroxide.

28. The method of claim **24** wherein said suitable solvent is aniline.

29. A method of producing one or more 4-ADPA intermediates comprising:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system; and

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and a controlled amount of protic material to produce one or more 4-ADPA intermediates;

wherein said suitable solvent is aniline, said protic material is water and the amount of protic material present at the beginning of the reaction is up to about 13.8 volume % water based on the total volume of the reaction mixture.

30. The method of claim **29** wherein aniline is reacted with nitrobenzene and said base is a tetraalkyl ammonium hydroxide.

31. The method of claim **30** wherein said tetraalkyl ammonium hydroxide is tetrabutyl ammonium hydroxide.

* * * * *

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Michael K. Stern et al	GROUP ART UNIT: 1209
SERIAL NO: Unknown	EXAMINER: Unknown
FILED: May 5, 1995	DATE: May 5, 1995
TITLE: Method of Preparing 4-Aminodiphenylamine	

I hereby certify that this correspondence is being deposited with the United States Postal Service as "Express Mail Post Office to Addressee" service under 37 CFR 1.10 Label No. RB995937164XUS in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C., 20231 on May 5, 1995
Kenneth D. Goetz
Registration No. 33,496

Kenneth D. Goetz DATE: 5/5/95

Preliminary Amendment

ASSISTANT COMMISSIONER OF PATENTS
WASHINGTON, D.C. 20231

Sir:

Please amend the above-identified application as follows and consider the following remarks.

In the Specification

Please amend the specification as follows:

Table 6, page 22, line 20, please delete "150" and insert therefor — 1.5 —.
Table 6, page 22, line 21, please delete "99" and insert therefor — 0.99 —.
Table 6, page 22, line 22, please delete "62" and insert therefor — 0.62 —.
Table 7, page 23, line 6, delete "4.7" and insert therefor — 4.3 —.
Table 7, page 23, line 7, delete "4.7" and insert therefor — 5.9 —.
Table 7, page 23, line 8, delete "4.7" and insert therefor — 9.6 —.

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B

In the Claims

Please amend the claims as follows:

1 ~~18.~~ (Amended) A method of producing one or more 4-ADPA intermediates comprising:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system; and

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and a controlled amount of protic material to produce one or more 4-ADPA intermediates [The method of Claim 1] wherein a desiccant is present during step (b) to control the amount of protic material present during the reaction of aniline or substituted aniline derivative and nitrobenzene.

3 ~~20.~~ (Amended) A method of producing one or more 4-ADPA intermediates comprising:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system; and

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and a controlled amount of protic material to produce one or more 4-ADPA intermediates [The method of Claim 1] wherein the amount of protic material in step (b) is controlled by the continuous distillation of said protic material.

5 ~~47.~~ (Amended) A method of producing 4-aminodiphenylamine (4-ADPA) or substituted derivatives thereof comprising:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system;

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone at a suitable temperature, and in

the presence of a suitable base and controlled amount of protic material to produce one or more 4-ADPA intermediates; and

c) reducing the 4-ADPA intermediates under conditions which produce 4-ADPA or substituted derivatives thereof [The method of Claim 24] wherein a desiccant is present during step (b) to control the amount of protic material present during the reaction of aniline or substituted aniline derivative and nitrobenzene.

74. (Amended) A method of producing 4-aminodiphenylamine (4-ADPA) or substituted derivatives thereof comprising:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system;

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and controlled amount of protic material to produce one or more 4-ADPA intermediates; and

c) reducing the 4-ADPA intermediates under conditions which produce 4-ADPA or substituted derivatives thereof [The method of Claim 24] wherein the amount of protic material in step (b) is controlled by the continuous distillation of said protic material.

91. (Amended) A method of producing alkylated p-phenylenediamines or substituted derivatives thereof comprising:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system;

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and controlled amount of protic material to produce one or more 4-ADPA intermediates;

c) reducing the 4-ADPA intermediates to produce 4-ADPA or substituted derivatives thereof; and

d) reductively alkylating the 4-ADPA or substituted derivatives thereof of step (c) [The method of Claim 49] wherein a desiccant is present during step (b) to control the amount of protic material present during the reaction of aniline or substituted aniline derivative and nitrobenzene.

11 69. (Amended) A method of producing alkylated p-phenylenediamines or substituted derivatives thereof comprising:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system;

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and controlled amount of protic material to produce one or more 4-ADPA intermediates;

c) reducing the 4-ADPA intermediates to produce 4-ADPA or substituted derivatives thereof; and

d) reductively alkylating the 4-ADPA or substituted derivatives thereof of step (c) [The method of Claim 49] wherein the amount of protic material in step (b) is controlled by the continuous distillation of said protic material.

Please add the following new claims:

13 84. The method of Claim 18 wherein said suitable base is selected from the group consisting of tetrasubstituted ammonium hydroxides, alkyl substituted diammonium hydroxides and mixtures thereof, wherein each substituent of said tetrasubstituted ammonium hydroxide is independently selected from alkyl, aryl or arylalkyl groups.

14 85. The method of Claim 84 wherein said suitable base is a tetrasubstituted ammonium hydroxide.

15 86. The method of Claim 85 wherein said tetrasubstituted ammonium hydroxide is a tetraalkyl ammonium hydroxide.

16 87. The method of Claim 86 wherein said tetraalkyl ammonium hydroxide is tetramethyl ammonium hydroxide.

17 88. The method of Claim 84 wherein said suitable solvent is aniline.

18 89. The method of Claim 20 wherein said suitable base is selected from the group consisting of tetrasubstituted ammonium hydroxides, alkyl substituted diammonium hydroxides and mixtures thereof, wherein each substituent of said tetrasubstituted ammonium hydroxide is independently selected from alkyl, aryl or arylalkyl groups.

19 90. The method of Claim 89 wherein said suitable base is a tetrasubstituted

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ammonium hydroxide.

91. The method of Claim 90 wherein said tetrasubstituted ammonium hydroxide is a tetraalkyl ammonium hydroxide.

92. The method of Claim 91 wherein said tetraalkyl ammonium hydroxide is tetramethyl ammonium hydroxide.

93. The method of Claim 89 wherein said suitable solvent is aniline.

94. A method of producing one or more 4-ADPA intermediates comprising:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system,

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone at a suitable temperature, and in the presence of a suitable base and protic material to produce one or more 4-ADPA intermediates, and

c) controlling the amount of said protic material in step (a) or (b) to provide a selectivity of at least 0.97, wherein the selectivity is the molar ratio of 4-ADPA intermediates to undesired products.

95. The method of Claim 94 wherein said suitable base is selected from the group consisting of tetrasubstituted ammonium hydroxides, alkyl substituted diammonium hydroxides and mixtures thereof, wherein each substituent of said tetrasubstituted ammonium hydroxide is independently selected from alkyl, aryl or arylalkyl groups.

96. The method of Claim 95 wherein said suitable base is a tetrasubstituted ammonium hydroxide.

97. The method of Claim 96 wherein said tetrasubstituted ammonium hydroxide is a tetraalkyl ammonium hydroxide.

98. The method of Claim 97 wherein said tetraalkyl ammonium hydroxide is tetramethyl ammonium hydroxide.

99. The method of Claim 95 wherein said suitable solvent is aniline.

100. A method of producing one or more 4-ADPA intermediates comprising:

a) bringing aniline or substituted aniline derivatives and nitrobenzene into reactive contact in a suitable solvent system; and

b) reacting the aniline or substituted aniline derivatives and nitrobenzene in a confined zone at a suitable temperature, and in

the presence of a suitable base and a controlled amount of protic material to produce one or more 4-ADPA intermediates;

wherein said suitable solvent is aniline, said protic material is water and the amount of protic material present at the beginning of the reaction is up to about 13.8 volume % water based on the total volume of the reaction mixture.

101. The method of Claim 100 wherein aniline is reacted with nitrobenzene and said base is a tetraalkyl ammonium hydroxide.

102. The method of Claim 101 wherein said tetraalkyl ammonium hydroxide is tetrabutyl ammonium hydroxide.

REMARKS

Claims 18, 20, 43, 45, 67 and 69 have been amended to remove the dependency on Claims 1, 24 and 49 by incorporating the limitations of canceled Claims 1, 24 and 49. Claims 84-102 have been added to more particularly claim applicant's invention. Support for "selectivity of 0.97" in new Claim 94 can be found in the specification at Example 15, page 28, choline hydroxide example. Support for the definition of selectivity and the term "undesired products" can be found in the specification at page 9, lines 1-2 and 18-25, page 10, lines 9-14, page 19, Table 2, third column and page 20, lines 33-36 which indicate that selectivity is based on the ratio of desired products, i.e. 4-ADPA intermediates, to undesired products, e.g. 2-nitrodiphenylamine, azobenzene and phenazine. Support for new Claims 84-87, 89-92 and 95-98 can be found in the specification at page 7, line 28 - page 8, line 2 and page 8, lines 7-10. Support for new Claims 88, 93 and 99 can be found in the specification at page 7, lines 5-8 and 12-15. Support for new Claims 100-102 can be found in the specification in Example 15. The calculation of the vol. % water present at the beginning of the reaction in Example 15 is provided in attached Appendix C. No new matter has been added by the amendment of the specification and claims or the addition of new claims.

Claims 18-21, 43-46, 67-70 and 84-102 are currently in the application for examination.

The amendments to page 22, Table 6 of the specification are to correct obvious

typographical errors. Since the limiting reagent in the reaction is nitrobenzene (1.9 mmole), it is clear that the yield of 4-ADPA intermediates must be less than 1.9 mmole. As such, applicants respectfully submit that it is clear that a decimal point was omitted in the mmole yields of Table 6 that have been amended. The amendment to Table 7, page 23, line 6 of the specification is to correct a typographical error in the % water. The amendment to Table 7, page 23, lines 7 and 8 of the specification is to correct errors made in the calculation of the amount of water. Since the first column of Table 7 is constant and the text at page 22, lines 30-31 states that the amount of protic material added to the reaction is kept constant, and since the tetramethylammonium hydroxide is used as a dihydrate in varying amounts, i.e. the amount of water added via the base varies, it is clear that the values in the second column of Table 7 are not constant but rather increase as the amount of base increases. Calculations of the % water in Table 7 are provided in attached Appendix B. Therefore, applicants respectfully submit that the amendments to the specification are not new matter and respectfully request that the amendments be entered.

The following is a discussion of the Stuehr et al, Frimer et al and Wohl references cited in the Information Disclosure Statements.

Stuehr et al disclose the reaction of aniline with superoxide in the presence of dimethyl sulfoxide as solvent and crown ether under "dry" conditions. Stuehr et al also disclose that oxygen is required for the reaction.

Stuehr et al does not disclose or suggest the process of the invention as claimed. Therefore, applicants respectfully submit that Claims 18-21, 43-46, 67-70 and 84-102 are clearly patentable over Stuehr et al.

Frimer et al disclose the reaction of aniline with nitrobenzene in benzene as solvent using potassium t-butoxide/crown ether as base under "dry" conditions.

Wohl (Chemische Berichte, 34, p. 2442 (1901)) discloses the reaction of aniline with nitrobenzene in aniline as solvent using NaOH as base under "anhydrous" conditions, and Wohl (Chemische Berichte, 36, p. 4135 (1903)) identifies the minor product of this reaction of aniline with nitrobenzene as p-nitrosodiphenylamine (p-NDPA). Therefore, applicants respectfully submit that Wohl (1901) and Frimer et al are equivalent references with respect to the invention as claimed and that both Wohl and Frimer teach processes that result in poor yields of 4-ADPA intermediates.

The major difference between Wohl (1901) and Frimer et al is that Frimer et

al conducted the reaction of aniline and nitrobenzene in the presence of a suitable base and a crown ether phase transfer catalyst. However, applicants respectfully submit that neither Wohl reference nor Frimer et al teach conducting the reaction of aniline and nitrobenzene in the presence of a controlled amount of protic material. In addition, neither Wohl reference nor Frimer et al teach conducting the reaction of a substituted aniline derivative and nitrobenzene in the presence of a controlled amount of protic material. It was applicants who discovered the criticality of controlling the amount of protic material present in the reaction of aniline or substituted aniline derivatives with nitrobenzene. Specifically, neither reference teach controlling the amount of protic material during the reaction by either use of a desiccant or continuous distillation.

Therefore, applicants respectfully submit that the process of Claims 18, 20, 43, 45, 67 and 69 patentably distinguish over Frimer et al and Wohl.

Applicants respectfully submit that Claim 94 further distinguishes over Frimer et al and Wohl. Claim 94 requires that the amount of protic material be controlled such that the selectivity is at least 0.97 wherein selectivity is the molar ratio of 4-ADPA intermediates to undesired products. The basis for the selectivity of 0.97 can be found in Example 15 as set forth above. The maximum selectivity taught by the Wohl and Frimer et al references is the selectivity in Frimer et al of 0.383. Calculations of selectivity are shown in attached Appendix A. Neither Frimer et al nor Wohl disclose or suggest a process which is capable of achieving the selectivity to 4-ADPA intermediates attainable with the claimed process. Therefore, controlling the amount of protic material present during the reaction to achieve a selectivity of at least 0.97 results in at least a 150 percent increase in selectivity to 4-ADPA intermediates. As such, applicants respectfully submit that Claim 94 is clearly patentable over Frimer et al and Wohl.

Applicants also respectfully submit that dependent Claims 84, 89 and 95 further distinguish over Frimer et al and Wohl. Dependent Claims 84, 89 and 95 require the base to be selected from tetrasubstituted ammonium hydroxides, alkyl substituted diammonium hydroxides, or mixtures thereof. Neither Frimer et al nor Wohl disclose or suggest using a tetrasubstituted ammonium hydroxide or alkyl substituted diammonium hydroxide as base. As such, use of tetrasubstituted ammonium hydroxides or alkyl substituted diammonium hydroxide as base patentably distinguish over Frimer et al and Wohl.

Applicants respectfully submit that Claims 100-102 further distinguish over Frimer et al and Wohl. Claim 100 requires that the reaction be conducted in aniline as the suitable solvent and that the vol. % water present at the beginning of the reaction is up to 13.8 volume percent. Frimer et al and Wohl teach starting with "dry" conditions, i.e. no protic material. Neither Frimer et al nor Wohl disclose or suggest conducting the reaction with a controlled amount of protic material of up to 13.8 volume percent. Therefore, applicants respectfully submit that Claims 100-102 are clearly patentable over Frimer et al and Wohl.

In view of the above remarks, applicants respectfully submit that Claims 18-21, 43-46, 67-70 and 84-102 are clearly patentable over Frimer et al and Wohl.

Examination and allowance of Claims 18-21, 43-46, 67-70 and 84-102 is respectfully requested.

Respectfully submitted,

5/5/95
Date

Kenneth D. Goetz, Attorney
Registration No. 32,696
Telephone No. (314) 694-3701

Monsanto Company
Mail Zone A3SA
800 N. Lindbergh Blvd.
St. Louis, Missouri 63167

APPENDIX A

Calculation of Selectivity

I. Basis for 0.97 Selectivity in claim 96:

Example 15 - choline hydroxide example

4-ADPA intermediates = 4-NODPA + 4-NDPA
undesired products = phenazine + azobenzene
Note: The small difference between sum of yields and nitrobenzene conversion is believed to be analytical.

Selectivity = (4-NODPA + 4-NDPA) / (phenazine + azobenzene)
= (33.0 + 9.6) / (0.85 + 43.2)
= 0.97

II. Calculation for Frimer et al.: (based on the 4th example in Table II)

(1) Aniline charged is 2.5 mmole and conversion is 85%; nitrobenzene is the limiting reagent at 75 mole % of aniline.

(2) A major amount of the nitrobenzene reacted cannot be accounted for as identified products (4-nitrodiphenylamine and azobenzene). This indicates that undesirable products other than azobenzene were generated in an amount equal to nitrobenzene converted minus known products.

(3) Azobenzene is assumed to be generated from one mole each of aniline and nitrobenzene.

(4) Example 3 of Table II indicates that some nitrobenzene is generated from oxidation of aniline at 0.04 mmole NB /mmole aniline reacted.

(5) Footnote c of Tables I and II indicates that up to 35% of nitrobenzene remaining may be lost during work-up.

(6) Calculation of known products:

(a) aniline converted = 0.85 (2.5) = 2.125 mmole
(b) 4-NDPA produced = 0.2 (2.125) = 0.425 mmole
(c) azobenzene produced = 0.064 (2.125) = 0.136 mmole

(7) Calculation of nitrobenzene converted:

(a) nitrobenzene in = 0.75 (2.5)	= 1.875 mmole
(b) nitrobenzene made = 0.04 (2.125)	= 0.085 mmole
(c) nitrobenzene available to react = 7(a) + 7(b)	= 1.96 mmole
(d) nitrobenzene in product = 0.13 (2.125)/0.65	= 0.425 mmole
(e) nitrobenzene converted = 7(c) - 7(d)	= 1.535 mmole
(f) unknowns undesirable products generated = 7(e) - 6(b) - 6(c)	= 0.974 mmole

(8) Selectivity = 6(b) / (6(c) + 7(f))

= 0.425 / (0.136 + 0.974) = 0.383

APPENDIX B

Calculation of Vol. % Water in Table 7

I. Run on line 1 of Table 7:

Aniline	2 mL	
Nitrobenzene	2 mL	
Water added	0.1 mL	
Base	0.33 mL	(The volume of base is calculated based on an approximate density of the base in the reaction mixture of 1 g/mL. ∴ 0.0025 mol base = 0.33 g base = 0.33 mL base)

Total volume of reaction mixture = 4.43 mL

Amount of water in base = (0.0025 mol base)(2 mol water/mol base)(18g/mol) = 0.09 g
Volume of water in base = (0.09 g)(1 g/mL) = 0.09 mL
Total water present in reaction mixture = 0.1 + 0.09 = 0.19 mL

Vol. % Water = (0.19 mL/4.43 mL) x 100 = 4.3 vol %

II. Run on line 2 of Table 7:

Aniline	2 mL	
Nitrobenzene	2 mL	
Water added	0.1 mL	
Base	0.66 mL	0.005 mol base / 0.0025 mol base = 2; 2 x 0.33 = 0.66

Total volume of reaction mixture = 4.76 mL

Amount of water in base = (0.005 mol base)(2 mol water/mol base)(18g/mol) = 0.18 g
Volume of water in base = (0.18 g)(1 g/mL) = 0.18 mL
Total water present in reaction mixture = 0.1 + 0.18 = 0.28 mL

Vol. % Water = (0.28 mL/4.76 mL) x 100 = 5.9 vol %

III. Run on line 3 of Table 7:

Aniline	2 mL	
Nitrobenzene	2 mL	
Water added	0.1 mL	
Base	1.65 mL	0.0125 mol base / 0.0025 mol base = 5; 5 x 0.33 = 1.65

Total volume of reaction mixture = 5.75 mL

Amount of water in base = (0.0125 mol base)(2 mol water/mol base)(18g/mol) = 0.45 g
Volume of water in base = (0.45 g)(1 g/mL) = 0.45 mL
Total water present in reaction mixture = 0.1 + 0.45 = 0.55 mL

Vol. % Water = (0.55 mL/5.75 mL) x 100 = 9.6 vol %

APPENDIX C

Calculation of Vol. % Water in Example 15

Assumption: Density of t-butylammonium hydroxide (TBA(H)) in reaction mixture is approximately 1 and density of reaction mixture is approximately 1.

F.W. TBA(H) = 259 g/mole

Charged 59 g of aqueous TBA(H):

0.091 mole TBA(H) x 259 g/mole = 23.6 g TBA(H)

Water present in base charged = 59 - 23.6 = 35.4 g water

Charged 55 g aniline

Total material in = 55 g aniline + 59 g base = 114 g total

Removed 35 mL : assume azeotrope is 70% water / 30 % aniline

Water removed = 35 mL x 1g/mL x 0.7 = 24.5 g water

Water remaining = 35.4 - 24.5 = 10.9 g water

% water at start of reaction = 10.9 g water / (114 g total - 35 g removed) = 10.9 / 79 = 13.8 %

PUBLIC VERSION

Exhibit 4:
Excerpts from Hearing Transcript

Proprietary In Its Entirety And Not Subject to Summarization

EPA/EPO/OEB
D-80298 München
+49 89 2399 - 0
TX 523 656 epmu d
FAX +49 89 2399 - 4465

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Generaldirektion 2 | Directorate General 2 | Direction Générale 2

Schalkwijk, Pieter Cornelis
AKZO NOBEL N.V.
Patent Department (Dept. APTA)
P.O. Box 9300
6800 SB Arnhem
PAYS-BAS

routs:
case:
Received: 20 JUN 2000
Akzo Nobel NV
Intellectual Property Department
Arnhem

Application No. / Patent No.	Ref.	Date
92 914 179.4-2103 / 0590053 /	ACD2615EP/OPP	16.06.00
Proprietor: FLEXSYS AMERICA L.P.		

Decision of revoking the European Patent (Article 102(1) EPC)

The Opposition Division - at the oral proceedings dated 23.05.2000 - has decided:

European Patent No. EP-B-0590053 is revoked.

The reasons for the decision are enclosed.

Possibility of appeal
This decision is open to appeal. Attention is drawn to the attached text of Articles 106 to 108 EPC.

appeal 47744
Term no : 07
Call-up : 2000 / 08 / 01
Exp.date: 2000 / 08 / 16

Grounds of Appeal 47745
Term no :
Call-up : 2000 / 08 / 16
Exp.date: 2000 / 10 / 16

Registered letter with advice of delivery
EPO Form 2331 02.99CSX

Opposition Division:

Chairman:	BUTKOWSKYJ-WALKIW T L
2nd Examiner:	MERCEY J M
1st Examiner:	JARDON ALVAREZ J

EUROPÄISCHES PATENTAMT - EUROPEAN PATENT OFFICE - OFFICE EUROPÉEN DES BREVETS

Moennich, G
Formalities Officer
Tel. No.: +49 89 2399-8034

Enclosure(s): 8 page(s) reasons for the decision (Form 2916)
Wording of Articles 106 - 108 (Form 2019)
X Minutes of oral proceedings

to EPO postal service: 13.06.2000

Registered letter with advice of delivery

I. Facts and submissions.

I. European Patent N° 0 590 053 incorporating 81 claims was granted to FLEXSYS AMERICA L.P. Akron, Ohio 44333(US) on 24.09.1997 (Bulletin 1997/39) on the basis of European Patent Application 92914179.4, filed on 27.03.1992.

II. An opposition was filed on 23.06.1998 with letter dated 19.06.1998 by Dr. Milan Petro, Pankuchova 5, SK-85104 Bratislava requesting the revocation of the Patent in its entirety, on the grounds that the subject-matter of the patent is not patentable within the terms of Articles 52 to 57 EPC (see Article 100(a) EPC). The Opponent also made a subsidiary request for oral proceedings.

In support of the Opposition the following documents were cited:

(E1) Ber. **1903**, *36*, 4135-8;
(E2) Ukrain. Chim. Zur. **1955**, *21*, 350-60 (and Chem. Abstr. **1955**, 14773hi);
(E3) Zur. Obscej Chim. **1953**, *23*, 1743-9 (and Chem. Abstr. **1953**, 6953a);
(E4) Zur. Obscej Chim. **1955**, *25*, 2161-70 (and Chem. Abstr. **1956**, 866d1bt);
(E5) Uspechi Chimii, **1955**, *24*, 313-45;
(E6) Zur. Obscej Chim. **1952**, *22*, 502-509 (and Chem. Abstr.**1953**, 2182d,e,f);
(E7) J. Org. Chem. **1983**, *48*, 1700-5;
(E8) Tetrahedron Letters **1990**, *31*, 3217-20 and
(E9) Angew. Chemie **1986**, *98*, 958-68

English translations of the documents E2 to E6 were filed on 18.02.1999.

III. The Patentee responded (letter dated 23.04.1999, filed 26.04.1999) to the opposition arguing that the subject-matter of the claims is novel and involves an inventive step over the cited prior art. The Patentee requested the rejection of the opposition and the maintenance of the patent as granted. As auxiliary request he also requested oral proceedings.

IV. With letter dated 28.06.1999 the Opponent filed further observations and insisted on his arguments essentially having regard to documents E1 and E7. He also

pointed to the lack of clarity of the claims and the description.

V. By letter dated 30.09.1999 the Patentee contested the arguments of the Opponent and maintained his requests.

VI. In an Official Communication dated 05.11.1999 the Opposition Division invited the parties to Oral Proceedings to be held on 23.05.2000.

VII. By letter dated 19.04.1999 the Opponent further commented on the claims of the patent especially on the expression "a controlled amount of protic material" as given in claim 1 of the patent.

VIII. With letter dated 20.05.2000 the Patentee filed the results of two series of additional experiments wherein the examples in accordance with E1 and E7 were duplicated and the reaction conditions were changed in several respects using a controlled amount of protic material.

IX. Oral proceedings were held on 23.05.2000.

The discussion during the oral proceedings focussed mainly on documents E7 and E1 and on the interpretation of claim 1 of the patent, especially on the expression "a controlled amount of protic material".

The Patentee also filed an auxiliary request embracing claims 24 to 72 of the patent as granted.

At the end of the oral proceedings the Chairwoman announced the decision that the European patent is revoked.

X. The claims serving as a basis for the present decision are:

- **main request**: claims 1 to 81 of the patent as granted;
- **auxiliary request**: claims 24 to 72 of the patent as granted.

* * * * *

II. Reasons for the decision.

1. The opposition meets the requirements of Articles 99 and 100 EPC as well as those of Rule 55 EPC.

MAIN REQUEST.

2. *Novelty* (Article 54 EPC).

2.1. Claim 1 of the opposed patent relates to a method of producing one or more 4-aminodiphenylamine intermediates (4-ADPA, which are defined on page 3, lines 37 - 38 as 4-nitrodiphenylamine, 4-nitrosodiphenylamine, the substituted derivatives and the salts thereof) by reacting (substituted) aniline and nitrobenzene in the presence of a suitable base at a suitable temperature wherein the reaction is carried out in the presence of a controlled amount of protic material.

2.2. The novelty of the patent is disputed by the Opponent having regard to documents E7 and E1.

Document E7 discloses a process for the preparation of 4-nitrodiphenylamine (4-NDPA) by reaction of nitrobenzene and aniline at ambient temperature in dry benzene in the presence of potassium t-butoxide (see Table II; see also footnote of Table I and page 1705, General Oxidation Procedure).

Document E1 discloses the reaction of aniline with nitrobenzene in the presence of dry sodium hydroxide at a temperature of 110-120 °C (see example bridging pages 4136 and 4137).

2.3. It is not disputed that both documents disclose processes including all the features of claim 1 of the patent with the exception of the feature that the reaction is carried out "in the presence of a controlled amount of protic material" which is not explicitly mentioned in said documents.

Thus with respect to novelty it only has to be decided how the expression "in the presence of a controlled amount of protic material" is to be interpreted. It should also be considered that when deciding on novelty of the subject-matter of a claim the broadest technically meaningful interpretation of a claim should be taken into account.

2.4. Interpretation of "controlled amount of protic material".

According to the Patentee such term must be interpreted as the fact that some measure has to be taken by the skilled person in order to ensure that a suitable amount of protic material is present. Thus the generation of water in the claimed process cannot be regarded as a way of controlling its amount. Furthermore the description on page 4, line 45 to page 5, line 32 describes that the controlled amount of protic material is an amount which lies between a minimum and a maximum, the appropriate amount of protic material depending on factors such as the type of solvent, the type and amount of base, base cation, etc. The controlled amount is an amount which allows the advantages of the claimed invention to be obtained, in particular to maintain the selectivity of the desired products. The description and examples clearly show different ways of controlling the amount of protic material such as the use as base of tetramethylammonium hydroxide dihydrate (see example 1) or the continuous azeotropic distillation of water utilizing the water/aniline azeotrope (see example 12).

On the contrary the Opponent interprets said expression as including any amount of protic material, as any reaction uses controlled amounts of reagents and merely by selecting of the reagents, solvents and reaction temperature a control of the amount of protic material takes place even if it is not explicitly mentioned. Thus, for the Opponent, control of the amount of protic material in the reaction is always done.

According to the Guidelines for examination in the EPO a claim should be read giving the words the meaning and scope which they normally have in the relevant art; furthermore the claim should be read with an attempt to make technical sense out of it (see Guidelines C-III 4.2.). Thus, although the word "controlled" could be literally interpreted as meaning "checked" or "verified", it is clear from the

description that the amount of protic material is not merely "checked" but "regulated" or "modified" during the process. The expression "a controlled amount of protic material" is then interpreted as including all the cases wherein the amount of protic material is "modified" during the process. As in the process of claim 1 water is produced, the presence of this water is not considered as "a controlled amount of protic material"; but if the amount of water produced in the reaction is modified, either by addition or by elimination, then it would result in a process wherein the amount of protic material is controlled.

2.5. In the process of E7 the water formed will react with the potassium t-butoxide to form potassium hydroxide and tert-butanol modifying the amount of protic material and in the process of E1 a reaction temperature of 110 -120 °C is used which would result in the elimination of water (distillation) from the reaction system. It is thus considered by the Opposition Division that the processes disclosed in documents E7 and E1 fall within the scope of claim 1 of the present application and therefore the subject-matter of claim 1 is not novel.

The above interpretation of the scope of claim 1 is further confirmed by example 5 of the patent in suit. In this example sodium hydroxide and potassium t-butoxide (see Table 4, entries 3 and 5) are used as bases under reaction conditions similar to those described in E1 and E7. It was therefore the intention of the Patentee to embrace the reaction conditions of these documents.

2.6. It has been argued by the Patentee a) that example 5 actually does not relate to an embodiment of the process in accordance with the invention and that it should be considered as a comparative example and b) that when a controlled amount of protic material was used in the claimed process better results are obtained.

This argumentation cannot be followed by the Opposition Division.
Concerning a): it is clear from example 5 that it should represent an embodiment of the invention as claimed (cf. line 1 wherein is stated that "this example illustrates various bases which can be utilized in the method of the present invention..."). The Patentee cannot choose a broad expression to define the scope of its claims and then argue that he actually does not intend to cover such processes.

Concerning b): It is not disputed that the claimed process, under specific reaction conditions, results in improved yield and selectivity of the desired products (see examples in the patent). However claim 1 is not limited to such specific reaction conditions and embraces the processes described in E1 and E7 as discussed above. The Patentee has had the opportunity to amend the claims to cover only the processes which yield the desired products with improved selectivity.

2.7. For these reasons the subject-matter of claim 1 of the main request is not novel.

AUXILIARY REQUEST.

3. *Novelty* (Article 54 EPC).

A method of producing 4-ADPA or substituted derivatives thereof by first preparing 4-ADPA intermediates (4-nitro and/or 4-nitrosodiphenylamines) and then reducing said intermediates to produce 4-ADPA as described in claim 24 is not disclosed in any of the documents E1 to E9 cited by the Opponent. As discussed above documents E1 to E7 relate to methods of preparation of nitro- and nitrosodiphenylamines but none of these documents disclose the further reduction of said nitro/nitroso derivatives.

Since during the Oral Proceedings the Opponent acknowledged the novelty of the auxiliary request, it is not necessary to comment further on this matter.

The subject-matter of the claims according to the auxiliary request is novel (Article 54 EPC).

4. *The closest state of the art.*

As set out in the introductory description of the present patent specification it is known to prepare 4-ADPA by way of nucleophilic aromatic substitution, wherein an aniline derivative replaces halide. This method involves preparation of a 4-ADPA intermediate followed by reduction of the nitro moiety. Commercial processes use mainly p-chloronitrobenzene as starting material (see page 2, lines 15 - 39). Such known processes are said to be disadvantageous due to the use of

aniline derivatives such as formanilide which requires additional manufacturing equipment and the use of p-chloronitrobenzene which results in the formation of halide that is both corrosive and appears in the waste stream.

The process according to claim 1 of the patent in suit differs from said known process in the use of aniline and nitrobenzene as starting materials for the formation of the 4-ADPA intermediates.

5. *Problem and solution.*

5.1. When starting from said state of the art and taking into account the above mentioned differences, the problem solved according to claim 24 of the present patent can be seen as to find an alternative process for the preparation of 4-ADPA wherein the use of aniline derivatives as starting materials and the halide formation in the waste stream is avoided.

5.2. This problem is solved by the process according to claim 24 by carrying out the process using aniline and nitrobenzene as starting materials to form 4-ADPA intermediates which are then reduced.

5.3. The Opposition Division is satisfied that this problem has been credibly solved by the process of claim 1. The examples in the patent show that 4-ADPA intermediates are obtained (see, for instance, example 1) and then reduced to the desired 4-ADPA (see examples 19 and 20; see also page 5, lines 45 - 57).

6. *Inventive step* (Article 56 EPC).

6.1. The question to be discussed for the assessment of inventive step is whether it was obvious for the skilled person in the light of the available prior art to prepare the 4-ADPA intermediates by the reaction of aniline and nitrobenzene.

6.2. As discussed above documents E1 and E7 already disclose processes for the preparation of 4-ADPA intermediates by reaction of aniline and nitrobenzene (see E1, page 4136 and E7 Table II). The skilled person wishing to avoid the use of chloronitrobenzene and aniline derivatives in the prior art processes discussed in

section 4 above, would then find in documents E1 and/or E7 an alternative process for the preparation of 4-ADPA intermediates. The 4-ADPA intermediates would then be reduced by the known methods to arrive at the claimed invention. Therefore the subject-matter of claim 24 does not involve an inventive step.

6.3. The Patentee argued that since E1 and E7 result in very low yields of the intermediate 4-NDPA, the person skilled in the art wishing to improve a known commercial process would not even have considered these documents. Further, documents E1 to E7 were old published prior art documents and if the claimed process were so obvious someone else should already have arrived at the process.

This argumentation cannot be followed by the Opposition Division. Although the claimed process embraces embodiments which give very good results, it also embraces the embodiments wherein the 4-ADPA intermediates have been prepared by the processes of E1 and E7. Therefore the improvement of the yield cannot justify the inventive step of the process. Moreover although in some cases a very old document should not be considered as the closest prior art, the fact that a document has been published some years before the date of the publication of the patent does not automatically imply that it cannot be used for the skilled person if he has a good reason to select its content. The state of the art is defined as comprising everything made available to the public, clearly without any time restriction.

6.4. For these reasons the subject-matter of claim 24 of the auxiliary request does not involve an inventive step.

7. *Decision.*

The opposed patent is therefore revoked under Article 102(1) EPC since, in the opinion of the Opposition Division, the grounds for opposition mentioned in Article 100(a) EPC prejudice the maintenance of the European Patent 0 590 053, because the subject-matter of claim 1 of the main request is not novel (see above 2.7) and the subject-matter of claim 24 of the auxiliary request does not involve an inventive step (see above 6.4.).

Darae Law & Patent
647-9 Korean Intelligence Center
Yeoksam-dong, Kangnam-gu, Seoul
Attorney for defendant (Appellee) [See original for barcode.] 135-080
Seung Moon Park

(No. 4 Division, Civil Department)

Case number Seoul Superior Court

2005 na 9175 Injunction for Patent Infringement

Scheduled date:

Judges in charge: No. 4 Civil Division Court clerk: See-dong Yu

Direct telephone: 530-1217 Fax: 592-3567

Email:

Seoul Superior Court

No. 4 Civil Division

Judgment

Case No.	2005 na 9175 Injunction for patent infringement
Plaintiff/Appellant	Flexsys America L.P. 260 Springside Drive, Akron, OH, U.S.A. Representative: David C Minc. Attorneys: Jung-soo Choi, Yo-soon Chung
Defendant/Appellee	Kumho Petrochemical Co. Ltd Kumho Building, Shinmoon-ro 1-ga 57 Jongro-gu, Seoul CEOs: Chang-ku Park, Wan-jae Kim, Hong-kee Kim Attorneys: Darae Law & Patent Seung-moon Park, Suk-min Park
Lower court judgment	Seoul Central District Court. 12.17.2004. Judgment 2004 ka hap 33075
Argument concluded	7.27.2005
Judgment entered	10.12.2005

DECISION

1. Plaintiff's appeal shall be entirely dismissed.

2. Plaintiff shall bear the costs of the appeal.

Purpose of Claim and Purpose of Appeal

The judgment by the lower courts shall be rescinded. The defendant shall be prohibited from production, use, assignment, lease of the products listed on No. 1 List or from import or assignment or agreement to lease said products (including exhibits of the products for assignment or lease). The defendant shall destroy the entire finished and semi-finished products listed on No. 1 List that are held by the defendant.

Reasons

1. Basic facts

A. The plaintiff, a manufacturer and seller of a variety of chemicals that are used for rubber products such as tires, is the holder of the patent on "A method to manufacture 4-aminodephenylamin" (hereinafter "4-ADPA") (Patent applied for: 11/16/1993. Patent registered: 12/11/1997. Patent registration number: 132,514; hereinafter, "the patent invention of this case").

B. The patent invention of this case manufactures (refer to Claims 1 through 23), using aniline or a substituted aniline derivative (hereinafter "aniline compound") as starting materials, 4-Nitrodiphenyl or its substituted derivative and/or 4-Nitrosodiphynyl or its substituted derivative and/or its salt (hereinafter "4-ADPA intermediate compound. In the meantime, it is referred to as an intermediate compound of p-nitrosodiphenylamine in the Description of the Invention. Of the 4-ADPA intermediate compound(s), aforementioned "4-Nitrosodiphynylamine" will be referred to as "4-NDPA" and p-Nitrosodiphynylamine as "p-NDPA"). This invention relates to manufacturing 4-ADPA or its

substituted derivative (Claims 24 through 48) wherein 4-ADPA is alkylated after reduction to manufacture p-phenyldiamine or its substituted derivative (hereinafter referred "PPD"). PPD is a type of ant-aging agent that helps products last longer by preventing oxidization of the rubber products such as tires (Claims 49 through 74). Claims 1, 24, and 49 describe as follows:

(1) Claim 1: A method to manufacture one or more intermediate compounds of 4-ADPA including the steps a) and b) below; a) An aniline compound(s) and nitrobenzene are contacted for reaction in a suitable solvent system; b) An aniline compound(s) and nitrobenzene are reacted in a limited (reaction) zone at a suitable temperature in the presence of a suitable base and a controlled amount of protic materials.

(2) Claim 24: A method to manufacture 4-ADPA or its substituted derivative including the steps a) through c) below; a) An aniline compound(s) and nitrobenzene are contacted for reaction in a suitable solvent system; b) An aniline compound(s) and nitrobenzene are reacted in a limited reaction zone at a suitable temperature in the presence of a suitable base and a controlled amount of protic materials to manufacture one or more 4-ADPA intermediate compounds; c) 4-ADPA intermediate compounds are reduced under the conditions wherein 4-ADPA or its substituted derivatives are manufactured.

(3) Claim 49: A method to manufacture alkylated PPD including the steps a) through d); a) Aniline compounds and nitrobenzene are contacted for reaction; b) An aniline compound(s) and nitrobenzene are reacted in a limited reaction zone at a suitable temperature in the presence of a suitable base and a controlled amount of protic materials to manufacture one or more 4-ADPA intermediate compounds; c) 4-ADPA intermediate compounds are reduced to manufacture 4-ADPA or its substituted derivatives; d) 4-ADPA or its substituted derivatives from step c) are alkylated after reduction.

C. In the meantime, Sinorgchem Co. Shandong located at No. 1, Beilhuan Road, Caoxian, Shandong, 274400, China (hereinafter "Sinorgchem")[ ]lt [ ]and applied for a patent on July 4, 2003 in China under the name "A method to manufacture 4-ADPA". Claim 1 of said invention is described below and the flowchart of the manufacturing process is described in Attachment No. 2:

Claim 1: A method to manufacture 4-ADPA using nitrobenzene and aniline as ingredients. Two types of compound catalysers, corresponding to condensation reaction and hydrogenization, are additionally used. The overall process is a continuous cycle comprised of five [sic] sequential steps, namely 1) condensation, 2) hydrogenization, 3) separation, recovery and reuse of compound bases, 4) separation, recovery and reuse of recycled powdered compound catalysers, 5) separation, recovery and reuse of solvents and aniline that were used for hydrogenization, and 6) refinement.

D. The defendant is primarily engaged in manufacturing, processing, and selling synthetic rubbers of its own products or those manufactured by third parties. The defendant imports 4-ADPA from Sinorgchem (which is manufactured by Sinorgchem) and alkylates them after reduction to manufacture and sell PPD products.

[Bases of acknowledgement] Uncontested facts, description in Exhibit A-1, Exhibit A-2, Exhibit A-3-2, and Exhibit A-5, and the tenor of argument.

2. Claims by each party and opinion

A. Claims by each party

(1) The plaintiff claims that the 4-ADPA manufacturing method employed by Sinorgchem falls within the scope of Claim 24 of the patent invention of this case as illustrated in each drawing of Attachments 2 and 3 for the following reasons: ① Aniline and nitrobenzene are the starting materials ② A base is used as the catalyser of condensation reaction ③ It uses a means to control the amount of water - a protic material ④ It manufactures 4-ADPA by reducing the products generated during the condensation step. The defendant has not only infringed Claim 24 of the patent invention of this case by importing 4-ADPA that was manufactured by a method as described above, but also infringed Claim 49 of the patent invention of this case by manufacturing and selling PPD products that have been manufactured by reductive alkylation of the imported 4-ADPA. Therefore, the plaintiff prays for injunction of such infringing acts as described in the purpose of claims.

(2) In reaction, the defendant dismisses the plaintiff's claims, which are made on the premise that Sinorgchem manufactures 4-ADPA using a method that infringes the plaintiff's patent, for the following reasons: ① The patent invention of this case had been widely known, common knowledge, prior to the application for patent; therefore, it lacks novelty and progressiveness. Besides, the description and the scope of claims are not specific enough to apply the invention; therefore, the scope of claims cannot be accepted. ② Even if the patent invention of this case were valid, 4-ADPA itself is a common knowledge material. Besides, there exists a variety of prior techniques as to the methods of manufacturing it. Therefore, there is no way of knowing which method Sinorgchem is using to manufacture it.

B. Opinion

(1) The content of the patent invention of this case and the characteristics of each claim in the scope of claims

Claim 1 of the patent invention of this case [the condensation step] focuses on reaction of aniline compound(s) and nitrobenzene (hereinafter "Element 1")-the starting materials-in the presence of an

suitable base (hereinafter "Element 2") and a controlled amount of a protic material (hereinafter "Element 3; Claim 24 (the condensation step + the reductive step) adds a process of reducing 4-ADPA intermediate compound(s) (hereinafter "Element 4"), which were generated by each Element; Claim 49 (the condensation step + the reductive step + the reductive alkylation step) adds a reductive alkylation' process of 4-ADPA (hereinafter "Element 5") to Elements 1 through 4.

Meanwhile, in the context of organic chemistry such as the patent invention of this case, reduction refers to "an reaction wherein the number of hydrogen atoms of a certain compound increases or the number of oxygen atoms thereof decreases." Here, Element 4 is considered a catalytic reduction wherein Element 4 is reduced to hydrogen in the presence of a catalyser; that is, the nitro group of 4-NDPA (-NO_2 or -NO) is reduced to NH_2. Furthermore, Element 4 is merely an added process, which is not qualified for a patent on its own, as said reductive reaction can be performed by a commonly known reduction method as described in the description of the patent invention of this case – "Such reductive reaction can be performed by a commonly-known reduction method such as by combining a hydride source, such as sodium borohydride, with carbon palladium or carbon platinum catalyser."

Moreover, reduction alkylation or reductive alkylation is "a reaction which alkylates ammonia, first and second amine, by means of reduction in aldehyde or keton." The description of the patent invention of this case also states as follows: "The reductive alkylation of 4-ADPA for the purpose of enhancing antiozonant can be performed by one of the various commonly-known methods." Therefore, Element 5 itself cannot be possibly accepted as a patent either as in the case of Element 4, it is merely an added process.

Accordingly, Claims 24 and 49, though each constitutes an independent claim, merely add a

common-knowledge technique, assuming that the Claim 1 of the patent invention of this case has patentability. Hence, the patentability of those claims is subject to patentability of Claim 1 of the patent invention of this case. So, for the purpose of determining whether the patent invention of this case is common knowledge, Claim 1 will become the focus of discussion.

(2) Purpose of the patent invention of this case and the scope of claims

The description of the patent invention of this case states the purpose of the invention as follows: The purpose of the present invention is to eliminate the problems of corrosion in the reaction container caused by a substituted halogen material or presence of such substituted halogen in the stream of waste material when reacting aniline and nitrobenzene directly using the conventional technique, as well as to provide a commercially beneficial manufacturing process that results in reduced production cost of 4-ADPA and a higher yield while being environmentally friendly at the same time. In the meantime, whereas the examples of the patent invention of this case suggest that the conversion rate of nitrobenzene, the degree of selectivity and the yield rate of the intermediate compounds of 4-ADPA vary according to the control of aerobic/anaerobic, the temperature, the concentration or volume of the reacting material, and the protic material such as water, they don't necessarily limit the scope of claims of the patent invention of this case by suggesting optimization of the conversion rate, the degree of selectivity and the yield of the intermediate compounds of 4-ADPA that are produced as a result of various types of reactions as described above.

If so, the core technical concept of the patent invention of this case is in the possibility of controlling the yields of the intermediate compounds of 4-ADPA by controlling the reaction conditions as described above. Then, it can be safely assumed that the improved yield of intermediate compounds of 4-ADPA in the patent invention of this case (optimization by controlling the conversion rate and the degree of selectivity) is merely secondary to the invention, therefore the improved yield itself beyond a certain degree does not necessarily constitute a scope of claims in the patent invention of this case.

(3) Novelty of the patent invention of this case

(A) The content of the referenced inventions

The academic article published by Wohl (Exhibit B-1. The invention described in this article will be hereinafter referred to as "comparison invention") about 1903, relates to compounds that are generated during the reaction of nitrobenzene and aniline in the presence of a base, and its reaction mechanism. The secondary products were discovered at the para position when aniline was present. In a specific example, aniline and nitrobenzene were mixed and reacted at 120-125℃. As a result, p-NDPA was found, which is one of the intermediate compounds of 4-ADPA.

(B) Comparison of the patent invention of this case with the comparison invention

The patent invention of this case and the comparison invention share commonalities in a sense that ①they both suggest a method to manufacture p-NDPA by directly reacting nitrobenzene and aniline through a base catalyser. As to this, however, the plaintiff argues as follows: Though the comparison invention produces p-NDPA, one of the intermediate compounds of 4-ADPA, it is nothing but a side reaction with a yield merely 3.3%. Besides, the major product (the target material) of the comparison invention is either phenazine or phenazine oxide whereas 4-ADPA intermediate compounds (4-NDPA and p-NDPA) are the major products of the patent invention of this case, therefore, quite different from the comparison invention. Nonetheless, as long as the patent invention of this case has wholly adopted the technical concept of the comparison invention and incorporated the essential reaction conditions (such as the temperature of the water beyond the boiling point, and minimization of a protic material in the scope of claims), one may not easily share the plaintiff's view simply because it was described as a

secondary reaction in the comparison invention. ② In terms of the effects of the invention, the patent invention of this case generates less environmental hazard as it directly uses aniline compounds and nitrobenzene as reaction materials. It also provides considerable economic benefits in terms of reduced manufacturing costs. Likewise, the comparison invention rightfully shares the effects of the patent invention of this case because it also directly uses aniline and nitrobenzene as reaction materials. ③ Both inventions also share commonalities in terms of the composition as described in Attachment 4 table.

However, the patent invention of this case includes Element 3, thus demonstrating a difference from the comparison invention. We will discuss this further in detail. The description of the patent invention of this case states as follows:

It is important to control the volume of the protic material that is present during the reaction. Normally, during a reaction in aniline, if the moisture content is over 4% H_2O, it would restrain the reaction between aniline and nitrobenzene to the point that the reaction itself becomes meaningless. If the moisture content is controlled under 4%, however, the reaction would proceed within the allowable method...(omission)...hence, the reaction according to the present invention can be performed in anhydrous conditions. A controlled amount of protic material, therefore, refers to about 4% H_2O based on the volume of the reaction compounds, which is the point when the volume restrains the reaction of aniline and nitrobenzene. ...(omission)...One may determine the maximum amount of the protic material corresponding to a specific catalyser, the type of base, the volume of base, the positive ion of base by applying the technical specifics of the present invention. The minimum amount of the protic material, which is required to maintain the selectivity of the desired products, varies according to the catalyser, the type of base, the volume of base, and the positive ion of base. One may also determine the minimum amount of the protic material by applying the technical specifics of the present invention.

As the amount of the protic material, which is present during reaction, is important, said material can be again added to a desirable amount as allowed under the conditions. The protic materials that are added again during the reaction, including but not limited to water and methanol, are commonly known to those skilled in the related field.

The description further suggests how to add and distill drying agents such as tetra methyl ammonium hydroxide dehydrate, calcium hydroxide, and sodium hydroxide (In Claims 18 and 20, this is added to the first paragraph, hence treating it as a separate scope of claims). In Example 3, when adding water to the mixture, the selectivity of the intermediate compounds of 4-ADPA displays a proportion relation to the amount of water for a few sections, then turns again to an inverse proportion relation whereas the yield consistently maintains an inverse proportion relation with water. Example 8 shows test results, which suggest an inverse proportion relation between the amount of water being added to the mixture and the conversion rate of nitrobenzene and the yield of the intermediate compounds of 4-ADPA. In addition, a multiple number of examples are introduced, suggesting how to use drying agents or distillation in order to remove protic materials.

Together with the information contained in the description of the invention, in view of the fact that Claim 1 of the patent invention of this case is a condensation reaction that produces intermediates of 4-ADPA as a water molecule of simple structure falls apart after reaction of aniline compound and nitrobenzene in the presence of a base, the configuration that controls the amount of protic materials such as water in the patent invention of this case increases the yield of the intermediate compounds of 4-ADPA by increasing the conversion rate of nitrobenzene by lowering the water content (which is generated during the reaction) below a certain level, which is after all the core technical concept.

Further, "protic material can be again added to a desirable amount as allowed under the conditions" in the description is more or less an additional explanation that applies to a situation when the content of protic material falls below the target level due to an excessive removal of protic materials. In the meantime, in light of the basic reaction type of the patent invention of this case or the description "hence, the reaction according to the present invention can be performed in anhydrous conditions," as well as the test results in Examples 3 and 8, the existence of "the minimum amount of the protic material, which is required to maintain the selectivity of the desired products" does not have much merits on its own apart from the yield of the intermediate compounds of 4-ADPA, which is largely affected by the conversion rate of nitrobenzene.

Based on the overall tenor of the arguments backed by Exhibits B Nos. 1, 2, 3, 4, 5, 10, 11, and 12, the condensation reaction that generates water as a side product of the reaction of aniline and nitrobenzene in the presence of sodium hydroxide is displayed with its equation in the comparison invention. At this time, sodium hydroxide acts as a drying agent as well as a base. Furthermore, because the reaction temperature goes beyond the water boiling point, the water generated by such reaction is continuously removed according to the sodium hydroxide and the reaction temperature, which results in minimizing the water - a protic material. A multiple number of academic articles published prior to the patent invention of this case, as well as chemical related patents, contain a technical concept suggesting that said type of condensation reaction, an equilibrium reaction, may eliminate water, a side product of such reaction, to restrain an inverse reaction while promoting a forward reaction by keeping out of the equilibrium according to the Le Chatelier Principle. The inventor of the patent invention of this case, in his own article, published on June 26, 1992, acknowledged that the reaction retraining effect by water was due to the effects to the equilibrium of the anilide ion that is formed as hydrogen is removed from aniline. The patent invention of this case includes a equilibrium reaction that generates water as a side product. Then, changing the yield of the target materials by controlling the protic materials such as water in such equilibrium reaction can be called a common-knowledge technique, easily conceivable by a person skilled in the art.

(C) Opinion

Based on the findings above, the patent invention of this case has the same starting materials, the same reaction materials and the same target materials as those of the comparison invention while using the same technical concept and the essential reaction conditions as those of the comparison invention. Further, the patent invention of this case merely added a common-knowledge technique, which is easily conceivable by a person skilled in the art. Its effects also fall within the scope of predictable range, thus lacking novelty (even if the novelty aspect were accepted, the patent invention of this case could be easily conceived by combining the comparison invention with the common-knowledge technique, thus making it very difficult to accept the novelty).

3. Conclusion

If so, Claim 1 of the patent invention of this case cannot be accepted due to a lack of novelty. Furthermore, Claim 24 and Claim 49, wherein a common-knowledge reduction reaction or reductive alkylation was added as a additional process, cannot not be accepted either due to a lack of novelty (even if the novelty aspect were accepted, an injunction claim could not be established due to a clear lack of novelty). The claim of this case, which is based on the premise that the defendant has infringed the plaintiff's patent by manufacturing and selling PPD, which is alkylated after reduction from the 4-ADPA imported from Sinorgchem Co., is therefore dismissed for a lack of ground. The judgment by the lower court is in accord with our decision, therefore, justified. The plaintiff's appeal is hereby dismissed for a lack of ground.

Presiding judge	Young-tae Kim
Judge	Jong-ho Kim
Judge	Joon-ho Kim

1. List

[seal]

4-aminodephenylamin (4-ADPA) manufactured according to the following steps: an aniline and nitrobenzene are contacted for reaction in a suitable solvent system; aniline and nitrobenzene are reacted in a limited reaction zone at a suitable temperature in the presence of a suitable base and a controlled amount of protic materials to manufacture one or more 4-aminodephenylamine (4-ADPA) intermediate compounds; 4-aminodephenylamine (4-ADPA) intermediate compounds are reduced under the manufacturing conditions of 4-aminodephenylamin (4-ADPA), plus p-phenyldiamine (PPD) manufactured by means of reductive alkylation of said 4-aminodephenylamine (4-ADPA) (including 4-aminodephenylamine (4-ADPA) manufactured by Sinorgchem Co., Shandong at No. 1 Beihuan Road, Caoxian , Chandong, 274400, China, plus p-phenyldiamine (PPD) manufactured from said product by the defendant). End. [seal]

2. Manufacturing Process Flowchart

The diagram below refers to the 4-aminodephenylamine manufacturing process flowchart.

Symbols: [seal]
1 – Powdered compound catalyser
2 – Hydrogenization solvent
3 – Recovery and reuse of compound base catalyser [seal]
4 – Recovery and reuse of recycled compound base catalyser
5 – Recovery and reuse of hydrogenization solvent
6 – Recovery and reuse of aniline

[illegible] Diagram

[See original document for drawing.]

Compound base catalyser
Nitrobenzene
Aniline

Condensation Hydrogenization Separation I

Refinement Separation II

4-ADPA

3 Manufacturing Process Flowchart

Aniline, Catalyser

Aniline layer

Nitrobenzene — Condensation

Water layer

Condensed liquid

Catalyser A recover — Recovered water + fresh water

Organic layer — Inorganic layer

[See original document for drawing.]

Hydrogenization — Post-treatment

Refinement

Residues — 4-ADPA — Aniline — [illegible] — Water

Fig. 1 4-ADPA Manufacturing Process by Sinorgchem Co
(No. 2 & No. 4 figures in Exhibit A-3 & No. 3 & No. 10 figures in Exhibit A-3)

4. Comparison with of the Patent Invention of This Case with the Comparison Invention 1

[seal]

Claims of the patent invention of the case	Description of the patent invention of the case	Comparison invention 1
a) in a suitable solvent system	There is no restriction on suitable solvent systems...(omission)...excess aniline as to the water content in nitrobenzene,...(omission)..., works as a solvent.	Existence of excess aniline as to the water content in nitrobenzene.
Aniline, substituted aniline derivative and nitrobenzene are contacted for reaction		Reaction of aniline and nitrobenzene
b) to manufacture one or more 4-ADPA intermediate compounds	4-ADPA intermediate compounds refer to 4-nitrodephenylamine, 4-nitrosodiphynylamine (and p-nitrosodiphenylamine) and its substituted derivatives and salt	4-nitrosodiphenylamine was found as a product.
Reacted in a limited (reaction) zone at a suitable temperature	The reaction is performed at a suitable temperature in a broad range of temperatures, e.g. in the range of -10℃~150℃ ...(omission)...	Reaction between 120℃~125℃
A suitable base	Suitable bases include but not limited to alkali metal such as sodium metal,... (omission)...	Sodium hydroxide*

* Sodium hydroxide is the most common compound of alkali metal sodium hydroxide.

This is the original copy.

10.12.2005

Seoul Superior Court

Court clerk See-dong Yu [seal]

Note on appeal

If you object to the judgment, you must file a notice of appeal within two weeks from the date of receipt of the original copy of the judgment with Seoul Superior Court (West Wing 2nd Floor, General Reception Area)

Forwarding No.: 7-7-2005-005643638
Date forwarded: October 04, 2005

To: In Jae Soh, New Korea International Patent Law Office
3rd Fl, Janghyun Building, 637-23 Yoksam-dong
Kangnam-gu, Seoul, Postal Code 135-909

Korea Intellectual Property Tribunal
Department 17
Service of a True and Same Copy of the Decision

Complainant	Name	Sinochem Company, Shandong, China
	Address	Beihue An Road 1, Shandong China, Kao Country, China
Agent	Name	In Jeh Cho
	Address	New Korea International Patent Law Office 3rd Fl, JangHyun Building, 637-23 Yoksam-dong, Gangnam-gu, Seoul
Respondent	Name	Flexsys America L.P.
	Address	260 Springside Dr. Akron, Ohoo, U.S.A.
Agent	Name	Soo Ghil Chang
	Address	Kim & Chang Patent Law Office 9th Fl.Heungkuk Life Insurance Bldg. 226 Shinmunro 1-ga, Jongro-gu, Seoul
Ruling No.		2004 Dang 766
Case description		Patent Registration No. 132514 Nullification Ruling

Sent
10. 05. 2005
Intellectual
Property
Tribunal

A true and same copy of the Decision related to above-noted ruling is hereby served.

Attachment 1 true and same copy of Decision End.

October 4, 2005

Presiding Judge Yoon Won [illegible] Lee [seal]

Receipt
No. -
10. 10. 2005
New Korea Int'l
Patent Law Office

1. The party who has lost in this ruling may appeal to the Patent Court within 30 days from the date when the certified copy of Decision is received.
2. When you file a document with the Korea Intellectual Property Office, the date of filing is based on the date the document is mailed out as stamped on the envelope. When you file a lawsuit with the Patent Court, this rule shall not apply. Accordingly, the party concerned must make sure that the Complaint arrives at the Court by the filing date.

Please contact Jong Ho Kim, the contact person in the Decision Administration Office, at 042) 481-5870 for any inquiry you may have. For forms or procedures, please contact the Patent Team Call Center at 1544-8080.

Korea Intellectual Property Tribunal
Department 17
Decision

Ruling No.	2004 Dang 766
Case Description	Patent Registration No. 132514 Nullification Ruling
Complainant	Sinochem Company Beihue An Road 1, Shandong China, Kao Country, China
	Agent Patent attorney Soo Jin Kim, Eui Seop Yoon Eunice Patent Law Office 17th Fl., Yoonick Bldg. 706-13 Yoksam-dong, Kangnam-gu, Seoul
	Agent Patent attorney In Jeh Cho (New Korea International Patent Law Office) 3rd Fl, Janghyun Building, 637-23 Yoksam-dong, Kangname-gu, Seoul
Respondent	Flexsys America L.P. 260 Springside Dr. Akron, Ohoo, U.S.A.
	Agent Patent attorney Mi Sung Shim, Soo Ghil Chang, Sung Min Choo Young Hwan Yang, Hee Jun Choi, Hyun Sook Han (Kim & Chang Patent Law Office) 9th Fl.Heungkuk Life Insurance Bldg. 226 Shinmunro 1-ga, Jongro-gu, Seoul Sub-agent Patent attorney Seok Yong Kang 14th Fl., Royal Bldg. Dangjoo-dong, Jongro-gu, Seoul

HOLDINGS

1. Claims 1–6, Claims 9–11, Claim 13, Claim 14, Claim 16, Claims 18–29, Claims 32–34, Claim 36, Claim 37, Claim 39, Claims 41–54, Claims 57–59, Claim 61, Claim 62, Claim 64, and Claims 66–72 of the Patent No. 132514 Invention shall be invalidated and, with respect to the remaining Claims, the application for trial of the subject case shall be dismissed.
2. Of the costs of trial & ruling, the Respondent shall bear the portion relating to 57/74 and the Complainant shall bear the portion relating to 17/74.

PURPOSE OF THE PETITION

1. The patent of the Patent No. 132514 Invention shall be invalidated.
2. The Respondent shall bear the costs of trial & ruling.

GROUNDS

1. Basic facts

Exhibit A-1 Patent Registry shows that the Patent No. 132514 Invention (hereinafter referred to as "the patent invention of this case") is an invention entitled as a method of manufacturing 4-aminodiphenylamine (hereinafter referred to as "4-ADPA"), which was filed for application as a U.S. Patent (Application No. 719876) with the U.S. Patent Office on June 21, 1991; and the priority right thereof was presented on the grounds of the above-noted patent application, and thus the International Patent application thereof (Application No. PCT/US1992/2232) was filed on March 27, 1992 under the Patent Cooperation Treaty, and thereafter, a translated copy of the above-noted international patent application was submitted to the Korean Intellectual Property Office (KIPO) on November 16, 1993 and registered on December 11, 1997. As indicated in the Scope of the Patent Claims on Exhibit A-2 Registered Patent Gazette, the abstract of the patent invention of this case is as follows:

Claim 1. A method of manufacturing one or more 4-ADPA intermediate compounds that contain a) and b) described below: (a) bring aniline or a substituted aniline derivative in contact with nitrobenzene for reaction in a suitable solvent medium system; and (b) have aniline or a substituted aniline derivative react with nitrobenzene in the presence of suitable bases and adjusted quantity of protic material within a limited (reaction) band at suitable temperature in order to manufacture one or more 4-ADPA intermediate compounds. (hereinafter referred to as 'Claim 1 of the patent invention of this case,' and other Claims shall be named in the identical manner.);

Claim 2. A method of manufacturing in Claim 1, wherein the suitable solvent system is selected from aniline, nitrobenzene, dimethyl sulfoxide, dimethyl formamide, N-methyl pyrrolidone, pyridine, toluene, hexane, ethylene glycol dimethyl ether, diisopropyl ethylamine or their compound;

Claim 3. A method of manufacturing in Claim 2, wherein the solvent is selected from aniline, dimethyl sulfoxide, dimethyl formamide and toluene;

Claim 4. A method of manufacturing in Claim 2, wherein the suitable solvent medium system contains a protic solvent medium;

Claim 5. A method of manufacturing in Claim 4, wherein the protic material is selected from methanol, water and their compound;

Claim 6. A method of manufacturing in Claim 1, wherein the solvent medium system contains water that amounts to 4v/v% of the total volume of aniline and the reaction compound;

Claim 7. A method of manufacturing in Claim 1, wherein the solvent medium system contains water that amounts to 8v/v% of the total volume of dimethyl sulfoxide and the reaction compound;

Claim 8. A method of manufacturing in Claim 1, wherein the solvent medium system contains methanol that amounts to 3v/v% of the total volume of aniline and the reaction compound;

Claim 9. A method of manufacturing in Claim 1, wherein the suitable temperature ranges from -10°C to 150°C;

Claim 19. A method of manufacturing in Claim 18, wherein the drying agent is selected from a group that is comprised of anhydrous sodium sulfate, molecular sieves (molecular sieves), tetramethyl ammonium hydroxide dehydrate, anhydrous potassium hydroxide, anhydrous sodium hydroxide and activated alumina;

Claim 20. A method of manufacturing in Claim 1, wherein the amount of the protic material in b) stage is controlled by continuous distillation of above-noted protic material;

Claim 21. A method of manufacturing in Claim 20, wherein the protic material is water and the water is removed by an azeotropic distillation (method) that uses water/aniline azeotropic material;

Claim 22. A method of manufacturing in Claim 1, wherein the substance of the substituted aniline derivative is selected from a group that is comprised of aryl group, Ar-alkyl base, and Arc-aryl base that contain halide, $-NO_2$, $-NH_2$, alkyl group, alkoxy group, $-SO_3$, -COOH and at least one $-NH_2$ group, and the halide is selected from a group that is comprised of chloride, bromide and fluoride;

Claim 23. A method of manufacturing in Claim 22, wherein the substituted aniline derivative is selected from a group that is comprised of 2-methoxy aniline, 4-methoxy aniline, 4-chloroaniline, p-toluidine, 4-nitro aniline, 3-bromo aniline, 3-bromo-4-amino toluene, p-amino benzoic acid, 2, 4-diamino toluene, 2, 5-dichloro aniline, 1, 4-phenylene diamine, and 1, 3, 5-triamino benzene;

Claim 24. A method of manufacturing 4-aminodiphenyamine (4-ADPA) or its substituted derivative that contain the steps of a)–c) described below: (a) bring aniline or a substituted aniline derivative in contact with nitrobenzene for reaction in a suitable solvent medium system; and (b) have aniline or a substituted aniline derivative react with nitrobenzene in the presence of suitable bases and adjusted quantity of protic material within a limited (reaction) band under

suitable temperature in order to manufacture one or more 4-ADPA intermediate compounds; and (c) reduce the 4-ADPA intermediate compounds under the condition that their substituted derivatives are manufactured;

Claim 25. A method of manufacturing in Claim 24, wherein the suitable solvent medium system is selected from aniline, nitrobenzene, dimethyl sulfoxide, dimethyl formamide, N-methyl pyrrolidone, pyridine, toluene, hexane, ethylene glycol dimethyl ether, diisopropyl ethylamine or their compound;

Claim 26. A method of manufacturing in Claim 25, wherein the solvent is selected from aniline, dimethyl sulfoxide, dimethyl formamide, toluene and their compound;

Claim 27. A method of manufacturing in Claim 25, wherein the suitable solvent medium system contains a protic solvent medium;

Claim 28. A method of manufacturing in Claim 27, wherein the protic material is selected from methanol, water and their compound;

Claim 29. A method of manufacturing in Claim 24, wherein the solvent medium system contains water that amounts to 4v/v% of the total volume of aniline and the reaction compound;

Claim 30. A method of manufacturing in Claim 24, wherein the solvent medium system contains water that amounts to 8v/v% of the total volume of dimethyl sulfoxide and the reaction compound;

Claim 31. A method of manufacturing in Claim 24, wherein the solvent medium system contains methanol that amounts to 3v/v% of the total volume of aniline and the reaction compound;

Claim 32. A method of manufacturing in Claim 24, wherein the suitable temperature ranges from -10°C to 150°C;

Claim 33. A method of manufacturing in Claim 24, wherein the suitable base is selected from an organic base and an inorganic base;

Claim 34. A method of manufacturing in Claim 33, wherein the above-noted organic

base and inorganic base contain alkali metal, alkali metal hydride, alkali metal hydroxide, phase-transition catalyst that is combined with the alkali source, amine, crown ether that is combined with the alkali source and their compound;

Claim 35. A method of manufacturing in Claim 24, wherein the base is selected from allyl ammonium salt, alkyl ammonium salt, allyl/alkyl ammonium salt and alkyl diammonium salt that are combined with the base source;

Claim 36. A method of manufacturing in Claim 24, wherein the base is mixed with aniline or a substituted aniline derivative to become a compound and this compound gets in contact with nitrobenzene for reaction;

Claim 37. A method of manufacturing in Claim 24, wherein aniline or a substituted aniline derivative is mixed with nitrobenzene to form a compound and the salt is added to this;

Claim 38. A method of manufacturing in Claim 24, wherein the solvent medium is aniline and the salt is tetra-alkyl ammonium hydroxide or alkyl-substituted diammonium hydroxide;

Claim 39. A method of manufacturing in Claim 24, wherein aniline or a substituted aniline derivative is reacted with nitrobenzene under an aerobic condition;

Claim 40. A method of manufacturing in Claim 24, wherein aniline or a substituted aniline derivative is reacted with nitrobenzene under an anaerobic condition;

Claim 41. A method of manufacturing in Claim 24, wherein a 4-ADPA intermediate compound is reduced with hydrogen in the presence of suitable catalyst;

Claim 42. A method of manufacturing in Claim 41, wherein the catalyst is carbon-phase platinum, carbon-phase palladium or nickel;

Claim 43. A method of manufacturing in Claim 24, wherein the drying agent exists during the b) reaction process in order to adjust the amount of protic material that exists while aniline or a substituted aniline derivative is reacted with nitrobenzene;

Claim 44. A method of manufacturing in Claim 43, wherein the drying agent is selected from a group that is comprised of anhydrous sodium sulfate, molecular sieves, tetramethyl ammonium hydroxide dehydrate, anhydrous sodium hydroxide, anhydrous potassium hydroxide and activated alumina;

Claim 45. A method of manufacturing in Claim 24, wherein the amount of the protic material in b) stage is controlled by continuous distillation of above-noted protic material;

Claim 46. A method of manufacturing in Claim 45, wherein the protic material is water and the water is removed by an azeotropic distillation (method) that uses water/aniline azeotropic material;

Claim 47. A method of manufacturing in Claim 24, wherein the substituent of the substituted aniline derivative is selected from a group that is comprised of aryl group, Ar-alkyl base, and Arc-aryl base that contain halide, $-NO_2$, $-NH_2$, alkyl group, alkoxy group, $-SO_3$, -COOH and at least one $-NH_2$ group, and the halide is selected from a group that is comprised of chloride, bromide and fluoride;

Claim 48. A method of manufacturing in Claim 47, wherein the substituted aniline derivative is selected from a group that is comprised of 2-methoxy aniline, 4-methoxy aniline, 4-chloroaniline, p-toluidine, 4-nitro aniline, 3-bromo aniline, 3-bromo-4-amino toluene, p-amino benzoic acid, 2, 4-diamino toluene, 2, 5-dichloro aniline, 1, 4-phenylene diamine, and 1, 3, 5-triamino benzene;

Claim 49. A method of manufacturing 4-aminodiphenyamine or its substituted derivative that contain the steps of a)–d) described below: (a) bring aniline or a substituted aniline derivative in contact with nitrobenzene for reaction in a suitable solvent medium system; and (b) have aniline or substituted aniline derivative react with nitrobenzene in the presence of suitable bases and adjusted quantity of protic material within a limited (reaction) band under suitable temperature in order to manufacture one or more 4-ADPA intermediate compounds; and (c) reduce the 4-ADPA intermediate compounds under the condition that their substituted derivatives are manufactured; and d) 4-ADPA or its substituted derivative described in c) is reduced and alkylated;

Claim 50. A method of manufacturing in Claim 49, wherein the suitable solvent system is selected from aniline, nitrobenzene, dimethyl sulfoxide, dimethyl formamide, N-methyl pyrrolidone, pyridine, toluene, hexane, ethylene glycol dimethyl ether, diisopropyl ethylamine or their compound;

Claim 51. A method of manufacturing in Claim 50, wherein the solvent is selected from aniline, dimethyl sulfoxide, dimethyl formamide, toluene and their compound;

Claim 52. A method of manufacturing in Claim 50, wherein the suitable solvent medium system contains a protic solvent medium;

Claim 53. A method of manufacturing in Claim 52, wherein the protic material is selected from methanol, water and their compound;

Claim 54. A method of manufacturing, in Claim 50, wherein the solvent medium system contains water that amounts to 4v/v% of the total volume of aniline and the reaction compound;

Claim 55. A method of manufacturing in Claim 50, wherein the solvent medium system contains water that amounts to 8v/v% of the volume of dimethyl sulfoxide and the reaction compound;

Claim 56. A method of manufacturing in Claim 50, wherein the above-noted solvent medium system contains methanol that amounts to 3v/v% of the volume of aniline and the reaction compound;

Claim 57. A method of manufacturing in Claim 50, wherein the suitable temperature ranges from -10°C to 150°C;

Claim 58. A method of manufacturing in Claim 50, wherein the suitable base is selected from an organic base and an inorganic base;

Claim 59. A method of manufacturing in Claim 58, wherein the above-noted organic base and inorganic base contain alkali metal, alkali metal hydride, alkali metal hydroxide, alkali

metal alkoxide, phase-transition catalyst that is combined with the salt source, amine, crown ether that is combined with the alkali source and their compound;

Claim 60. A method of manufacturing in Claim 50, wherein the base is selected from allyl ammonium salt, alkyl ammonium salt, allyl/alkyl ammonium salt and alkyl diammonium salt that are combined with the base source;

Claim 61. A method of manufacturing in Claim 50, wherein the base is mixed with aniline or a substituted aniline derivative to become a compound and [this compound] gets in contact with nitrobenzene for reaction;

Claim 62. A method of manufacturing in Claim 50, wherein aniline or a substituted aniline derivative is mixed with nitrobenzene to form a compound and the salt is added to this;

Claim 63. A method of manufacturing in Claim 50, wherein the solvent medium is aniline and the salt is tetra-alkyl ammonium hydroxide or alkyl-substituted diammonium hydroxide;

Claim 64. A method of manufacturing in Claim 50, wherein aniline or a substituted aniline derivative is reacted with nitrobenzene under an aerobic condition;

Claim 65. A method of manufacturing in Claim 50, wherein aniline or a substituted aniline derivative is reacted with nitrobenzene under an anaerobic condition;

Claim 66. A method of manufacturing in Claim 49, wherein 4-ADPA or its substituted derivative is reductively alkylated with ketone selected from a group that is comprised of acetone, methyl lisobutyl ketone, methyl isoamyl ketone and 2-octanone;

Claim 67. A method of manufacturing in Claim 49, wherein the drying agent exists during the b) reaction process in order to adjust the amount of protic material that exists while aniline or a substituted aniline derivative is reacted with nitrobenzene;

Claim 68. A method of manufacturing in Claim 67, wherein the drying agent is selected from a group that is comprised of anhydrous sodium sulfate, molecular sieves, tetramethyl ammonium hydroxide dehydrate, anhydrous potassium hydroxide, anhydrous sodium hydroxide and activated alumina;

Claim 69. A method of manufacturing in Claim 49, wherein the amount of the protic material in b) stage is controlled by continuous distillation of above-noted protic material;

Claim 70. A method of manufacturing in Claim 69, wherein the protic material is water and the water is removed by an azeotropic distillation (method) that uses water/aniline azeotropic material;

Claim 71. A method of manufacturing in Claim 49, wherein the substituent of the substituted aniline derivative is selected from a group that is comprised of aryl group, Ar-alkyl base, and Arc-aryl base that contain halide, $-NO_2$, $-NH_2$, alkyl group, alkoxy group, $-SO_3$, -COOH and at least one $-NH_2$ group, and the halide is selected from a group that is comprised of chloride, bromide and fluoride;

Claim 72. A method of manufacturing in Claim 71, wherein the substituted aniline derivative is selected from a group that is comprised of 2-methoxy aniline, 4-methoxy aniline, 4-chloroaniline, p-toluidine, 4-nitro aniline, 3-bromo aniline, 3-bromo-4-amino toluene, p-amino benzoic acid, 2, 4-diamino toluene, 2, 5-dichloro aniline, 1, 4-phenylene diamine, and 1, 3, 5-triamino benzene;

Claim 73. Diammonium salt that was alkylation substituted from 4-nitrodiphenylamine or 4-nitrosodiphenylamine: Here, each alkylation substituent of alkylation substituted diammonium ions is independently selected; and

Claim 74. A salt, as described in Claim 82 [sic], that is selected from a group comprising 4-nitrodiphenylamine bis-dibutylether hexamethylene diammonium salt and 4-nitrosodiphenylamine bis-dibutylethyl hexamethylene diammonium salt.

2. Claims of the Parties Concerned

A. Argument of the Complainant

The Complainant was seeking a decision as indicated in the purpose of this petition, and submitted Exhibits A-1~A-17 and Reference Material 1 citing the following points as core reasons:

(1) Claim 1 of the patent invention of this case relates to a method of manufacturing "4-Nitrodediphenylamine (referred to as '4-ADPA' hereinafter), 4-Nitrosodiphenylamine (hereinafter referred to as 'p-NDPA'), or their substituted derivatives, or their sodium (hereinafter generally referred to as '4-ADPA intermediate compound') by reacting aniline or a substituted aniline derivative with nitrobenzene. However, since the method of manufacturing p-NDPA which is one of 4-ADPA intermediate compounds by reacting aniline and nitrobenzene is publicly disclosed in Exhibit A-4 (Chem. Ber., 36, 1903, Whol A., page 4135-4138; referred to as 'the compared invention' hereinafter), a publication circulated prior to the date when the priority right of the patent invention of this case was claimed, Claim 1 of the patent invention of this case and its subordinate claims, Claims 2~23 of the patent invention of this case are either identical as the compared invention or an invention that can be easily derived from [the compared invention], and thus their registration violates provisions set forth in Section 29 Paragraph 1 or Paragraph 2 of the old Patent Law (Law prior to its revision to Law No. 4594 on December 30, 1993, and said law [is referred to] hereinafter);

(2) Claims 24~48 of the patent invention of this case relate to a method of manufacturing 4-ADPA or its substituted derivative by reducing the 4-ADPA intermediate compounds manufactured in the Claim 1 of the patent invention of this case, and Claims 49~72 of the patent invention of this case relate to a method of manufacturing p-phenylenediamine (referred to PPD hereinafter) or its substituted derivates by alkalizing 4-ADPA. However, since the method of reduction and alkylation is a publicly disclosed method in the concerned art even before the patent application of the patent invention of this case was submitted, Claim 24~Claim 72 of the patent invention of this case are either identical as the compared invention or an invention that can be easily derived from [the compared invention], and thus their registration violates provisions set forth in Section 29 Paragraph 1 or Paragraph 2 of the old Patent Law;

(3) Claims 73~74 of the patent invention of this case relate to sodium of compounds manufactured by the manufacturing method of the patent invention of this case.

However, manufacturing such sodium is very easy for anyone who is skilled in the art, [Claims 73 and 74 of the patent invention of this case] were filed in violation of provisions of Section 29 Paragraph 2 of the old Patent Law;

(4) The reaction presented in the compared invention is an equilibrium reaction; and by applying Le Chatelier's Principle to this [reaction], the patent invention of this case can be easily derived; and

(5) Among the components of Claim 1 of the patent invention of this case, "suitable base" and "in the presence of adjusted quantity of protic material" are ambiguous expressions with an overbroad meaning, hence violate provisions of Section 42, Paragraph 3 and Paragraph 4 of the old Patent Law.

B. Argument of the Respondent

The Respondent was seeking a decision to the effect that "Court decision for the petition on this case shall invalidate [such a petition]. The costs of trial & ruling shall be borne by the Complainant," and submitted Exhibit B-1~Exhibit B9 and Reference Material 17 citing the following points as core reasons:

(1) Claim 1 of the patent invention of this case is different from the compared invention in that the 4-ADPA intermediate compound is obtained by a reaction "in the presence of adjusted quantity of protic material," and even when Le Chatelier's Principle is combined with the compared invention, Claim 1 of the patent invention of this case can never be achieved;

(2) Since the compared invention belongs to "a different art for the invention" compared to Claim 24 and Claim 49 of the patent invention of this case, one cannot deny the inventiveness of Claim 24 and Claim 49 of the patent invention of this case;

(3) Since the specification of the patent invention of this case includes description sufficient for anyone who is skilled in the art to clearly understand the contents of the invention and replicate the invention, and illustrates various bases including tetraalkyle ammonium and hydroxide (TMAH) in addition to preferred embodiments, "suitable base" among the components of Claim 1 of the patent invention of this case satisfies a descriptive requirement for a specification; and

(4) Since the meaning of "adjustment" and how much amount is "adjusted quantity" are sufficiently described enough for anyone who is skilled in the art to clearly understand and replicate [the invention], "in the presence of adjusted quantity of protic material" among the components of Claim 1 of the patent invention of the case satisfies a descriptive requirement for a specification.

3. Is the Complainant an Interested Party?

Since the description in Exhibit A-3 (Warning) is indicative of the fact that the Complainant was indirectly encountering confrontation of rights from the Respondent, which suggests that [the Complainant] has interest in whether or not the patent invention of this case can continue to exist, the petition for decision of this case shall be acknowledged as a legitimate petition by an interested party.

4. Description of the Compared Invention.

The compared invention, an invention that directly reacts nitrobenzene and aniline in the presence of alkali in order to examine their reaction mechanism, describes that with aniline and nitrobenzene used as starting materials, a surplus amount of aniline is left against the mole content of nitrobenzene and they [aniline and nitrobenzene] are mixed with sodium hydroxide; and then the mixture is reacted at a temperature of 120~125 °C to create p-NDPA, one of 4-ADPA intermediate compounds.

5. Decision of this Court

A. Decision on whether or not the description in the specification is insufficient

The Complainant argues that of the components of Claim 1 of the patent invention of this case, "suitable base" and "in the presence of adjusted quantity of protic material" are ambiguous expressions with an overbroad meaning, therefore, inadequate descriptions. This court will now examine the Complainant's argument to that effect.

The scope of a patent invention needs to be evaluated not only by what is described in the claimed scope of the patent, but also by looking at the entire description covering detailed descriptions of the invention plus brief descriptions of drawings in order to clarify the nature and the purpose of the invention, and then form a judgment of the scope of the invention for its substance taking into consideration the invention's nature and purpose. Therefore, if the content of the invention that was filed for a patent application can be easily understood and replicated by anyone who has general knowledge in the concerned art, although there are partially ambiguous portions, [the description of the invention] should be seen as a legitimate description of the claimed scope (refer to Supreme Court Ruling 94 *Hu* 944 Decision on October 13, 1995). Hence, first of all, when "suitable bases" is examined from this point of view, as described in the detailed description of the patent invention of this case, " Suitable bases include, although not limited to, organic bases and non-organic bases such as alkali metals, ---(cut off)---, hydroxides, [illegible] and their compounds," types of bases are not specified but simply listed as examples; therefore, "suitable bases" of the components of Claim 1 of the patent invention of this case are necessary bases for manufacturing 4-ADPA intermediate compounds using aniline and nitrobenzene as staring materials and cannot be deemed particularly restricted in terms of type. Furthermore, since preferred embodiments of the patent invention of this case present examples of manufacturing 4-ADPA intermediate compounds using a variety of bases that encompass non-organic and organic bases such as tetrabutyl ammonium hydroxide, tetrapropyl ammonium hydroxide, benzyl trimethyl ammonium hydroxide, 18-crown-6 + 2KOH, and bis-dibutyl ethyl hexamethylen di-ammonium hydroxide in addition to the famous base of TMAH, anyone who is skilled in the art can easily select a base and replicate the patent invention of this case, hence, above-noted "suitable bases" satisfy the descriptive requirement of the claimed scope of the invention.

Next, when we examine "adjusted quantity of protic material," as the detailed description of the invention of this case describes, "The adjusted content of protic material refers to approximately 4% H_2O based on the total volume of the reaction compound when aniline is used as a solvent medium, in other words, the amount that suppresses the reaction between aniline and nitrobenzene.

This amount will be different depending on the upper limit of a solvent medium for the content of protic material that is present during the reaction. For instance, when DMSO is used as a solvent medium, and tetramethyl ammonium hydroxide is used as a base, the upper limit of the amount of protic material that is present during the reaction is approximately 8% H_2O," one can say that the allowed content of protic material depends on a base or a solvent medium. However, considering the types of base and solvent medium described in the detailed description of the patent invention of this case are generally selected ones in the concerned art, it can be acknowledged that anyone who is skilled in the art can easily determine the adjusted quantity of protic material without engaging in undue experiments; hence the argument of the Complainant who finds fault at this does not have grounds.

B. Decision on Inventiveness of the Patent Invention of This Case

(1) Claim 1 of the patent invention of this case

Claim 1 of the patent invention of this case and the compared invention have something in common in that both provide a method of manufacturing p-NDPA by reacting nitrobenzene and aniline.

In terms of technological construction in order to achieve such an objective, as Claim 1 of the patent invention of this case presents the following method as its key construction; ① in a suitable solvent medium system ② using aniline or a substituted aniline derivative and nitrobenzene as starting materials, ③ react above-noted starting materials within a limited (reaction) band at a suitable temperature ④ with a suitable base ⑤ in the presence of adjusted quantity of protic material ⑥ in order to manufacture more than one 4-ADPA intermediate compounds, we will examine above-reference method in comparison to the corresponding construction of the compared invention.

Since Component ① of Claim 1 of the patent invention of this case specifies the solvent medium system to "suitable," it cannot be viewed as putting specific limitation on a solvent medium system. Furthermore, the detailed description of the patent invention of this case describes, "A suitable solvent medium system includes, although not limited to, solvent mediums such as dimethyl sulfoxide, N-methyl pyrrolidone, dimethyl formamide, aniline, ------(cut off) ------, diisopropyl ethylamine or their compounds.

Desirably, -----(cut off)------, aniline or a substituted aniline derivative of surplus amount against the mole content of nitrobenzene plays the role of a solvent medium," which indicates Component ① of Claim 1 of the patent invention of this case includes aniline; since in the case of the compared invention, the surplus amount of aniline exists as well against the mole content of nitrobenzene, which indicates aniline is also used as a solvent medium, it appears that Component ① of Claim 1 of the patent invention of this case is publicly disclosed in the compared invention.

And Construction ② of Claim 1 of the patent invention of this case, when compared to starting materials of the compared invention, is identical as the compared invention in that it uses aniline and nitrobenzene as starting materials; Construction ③ and Construction ④ relate to reaction temperatures and bases, and the detailed description of the patent invention of this case shows that they include the temperature of 120~125 °C and sodium hydroxide as the base just as in the compared invention; furthermore, Construction ⑥ of the patent invention of this case includes p-NDPA, the created product of the compared invention. In conclusion, Construction ②, Construction ③, Construction ④, and Construction ⑥ of the patent invention of this case are publicly disclosed in the compared invention.

On the other hand, as to Construction⑤ of the patent invention of this case, a difference lies in the fact that while it reacts [the starting materials] in the presence of adjusted quantity of protic material, the compared invention does not explicitly describe such condition. In order to compare the above-noted difference between both inventions, first we shall examine whether or not a protic material is present in the compared invention, and then if a protic material is present in the compared invention, we shall examine if there is a noticeable difference between [the protic material of the compared invention] and the "adjusted quantity" of Claim 1 of the patent invention of this case.

The compared invention was for manufacturing p-NDPA, one of 4-ADPA intermediate compounds by reacting nitrobenzene and aniline and it is a publicly disclosed knowledge that through the reaction mechanism, water (H_2O), in addition to p-NDPA, becomes generated and water is one of representative protic materials. The reaction between nitrobenzene and aniline takes place in the form of minute molecule units and the number of molecules that exists is the same as the number of Avogadro per 1 mole of reactant (6.02×10^{23});

once a pair of molecules react for the first time, immediately water molecules become created, after which adjacent molecules react in the presence of water that is being created in a chain reaction. Therefore, since almost all molecules, unless they are completely removed at the same time water is produced, will react in the presence of water which is a protic material, one can say water which is a protic material is present in the compared invention.

Next, we shall examine 'adjusted quantity' of the protic material of the components of Claim 1 of the patent invention of this case. The detailed description of the patent invention of this case describes, "It is important to control the content of protic material that is present during the reaction. Generally, when reacting in the presence of aniline, the moisture that exists over approximately 4% H_2O suppresses the reaction between aniline and nitrobenzene to the degree that the reaction itself is made insignificant. As a result, when the content of the moisture is reduced below 4%, the reaction progresses within the allowable parameter. ---- (cut off) ------- Therefore, the reaction according to this invention can be executed in an anhydrous condition. The adjusted content of protic material refers to approximately 4% H_2O based on the total volume of the reaction compound when aniline is used as a solvent medium, in other words, the amount that suppresses the reaction between aniline and nitrobenzene," which indicates to us that 'adjusted quantity' of the protic material is to adjust water below a certain amount. However, the only description given to the lower limit is "the minimum quantity of protic material necessary to maintain the selectivity of the desired created product changes depending on a solvent medium, types of a base, the amount of a base, or positive ions of a base," which makes it impossible for us to easily find out what the lower limit is. In conclusion, it can be interpreted that while the lower limit of 'the adjusted quantity' in Claim 1 of the patent invention of this case may differ depending on a solvent medium, a base, or types of protic material, presence of the smallest amount of protic material would suffice as long as the reaction takes place.

As have been examined so far, although a certain amount of water, a protic material, becomes generated in the compared invention, it will evaporate or be absorbed due to a high reaction temperature and sodium hydroxide, and thus the content of water will be

extremely miniscule; when compared, the 'adjusted quantity' of the protic material of Claim 1 of the patent invention of this case also includes a minimum amount of water, hence, Construction ⑤ of Claim 1 of the patent invention of this case cannot be regarded as significantly different from the compared invention.

Lastly, in comparing the effect of both inventions, Claim 1 of the patent invention of this case does not use halide, but directly uses aniline and nitrobenzene in manufacturing the 4-ADPA intermediate compound, which has an effect of resolving problems such as environmental pollution, corrosion of the reactor, and high manufacturing costs. Since the compared invention also has aniline directly react with nitrobenzene, both inventions are identical in that they produce effects of resolving problems such as environmental pollution. The Respondent claims that Claim 1 of the patent invention of this case shows up to a 88% yield of the 4-ADPA intermediate compounds while the compared invention results in merely a 3.3% yield, and therefore there is a significant difference in the effects between the two invention. However, in the case of the 88% yield, it is merely one preferred embodiment that represents the maximum yield in Claim 1 of the patent invention of this case, and cannot be viewed as an effect that represents the entire construction of Claim 1 of the patent invention of this case which is claiming a far greater scope than that of the preferred embodiment; hence, it cannot be acknowledged that there are significant differences in the effects between Claim 1 of the patent invention of this case and the compared invention.

Accordingly, since the construction of Claim 1 of the patent invention of this case includes components that are publicly disclosed in the compared invention, and portions that have no difference in the construction cannot be acknowledged for their inventiveness, Claim 1 of the patent invention of this case is an invention that does not have inventiveness compared to the compared invention.

(2) Claim 24 and Claim 49 of the patent invention of this case

Claim 24 of the patent invention of this case involves a method of manufacturing 4-ADPA after first manufacturing 4-ADPA intermediate compounds in the same manner as in Claim 1 of the patent invention of this case and then reducing [the 4-ADPA intermediate

compounds], and Claim 49 of the patent invention of this case relates to a method of manufacturing PPD after first manufacturing 4-ADPA in the same manner as in Claim 1 of the patent invention of this case and then having [4-ADPA] go through a reductive alkylation process. As such, Claim 24 and Claim 49 of the patent invention of this case are after all components of Claim 1 of the patent invention of this case plus the reduction process and the reductive alkylation process added respectively, which we shall examine in the following paragraphs.

In general, reduction means, "a reaction in which the number of hydrogen atoms are increased or the number of oxygen atoms are decreased in a compound," and above-noted reduction process corresponds to a contact reduction method thereof where [materials] become reduced to hydrogen in the presence of a catalyst, in other words, a nitro group ($-NO_2$) of 4-NDPA or a nitro group of p-NDPA (-NO) is reduced to NH_2. As described in the detailed description of the patent invention of this case, "This reduction reaction can be executed through publicly disclosed reduction methods such as the one combining a hydride source, i.e., Sodium Borohydride, with a carbon-supported palladium catalyst or a carbon-supported platinum catalyst for use," the afore-mentioned reduction process is a publicly known technology in the concerned art and is not something that brings difficulty or particular enhancement effects when combined with Claim 1 of the patent invention of this case, and thus it is no more than a simple supplementary process for anyone who is skilled in the art to easily select.

In addition, reductive alkylation is "a reaction in which ammonia, the primary ammine, or the secondary ammine is alkylated in a reductive manner in aldehyde or ketone," and the detailed description of the patent invention of this case describes, "the reductive alkylation reaction of 4-ADPA in order to raise antiozonant can be executed by one of many publicly disclosed methods." Therefore, this process, just as in the case of the reduction process, is no more than a simple supplementary process for anyone who is skilled in the art to easily select.

Hence, since Claim 24 and Claim 49 of the patent invention of this case are nothing but simply adding publicly disclosed technology to Claim 1 of the patent invention of this case, as long as there is no inventiveness found in Claim 1 of the patent invention of this case, they are regarded as being easily invented from the compared invention.

(3) Subordinate claims of Claim 1, Claim 24 and Claim 49 of this case

(A) Claims 2~6, Claims 25~29 and Claims 50~54 of the patent invention of this case are subordinate claims that specified "a suitable solvent medium system" among components of Claim 1, Claim 24, and Claim 49 of the patent invention of this case, and they are limiting [the suitable solvent medium system] to aniline and water among others. However, they are identical with the compared invention in that the compared invention also uses aniline as a solvent medium and water is produced during the reaction.

(B) The temperature range of -10°C~150°C in Claim 9, Claim 32, and Claim 57 of the patent invention of this case falls under the same range as that of 120°C~125°C in the compared invention.

(C) Bases of Claim 10, Claim 11, Claim 33, Claim 34, Claim 58 and Claim 59 of the patent invention of this case include sodium hydroxide, which is the base of the compared invention.

(E) While Claim 13, Claim 14, Claim 36, Claim 37, Claim 61 and Claim 62 of the patent invention of this case relate to the combination sequence of materials, since there are no differences of effects depending on the combination sequence, it is merely a simple design change.

(F) Favorable conditions of Claim 16, Claim 39, and Claim 64 are not much different in comparison to the reaction conditions of the target.

(G) Claims 18~21, Claims 43~46 and Claims 67~70 of the patent invention of this case choose and specify methods such as a drying agent or azeotropic distillation in order to adjust content of water. However since the compared invention also employs anhydrous sodium hydroxide which is suggested as one of drying agents in the patent invention of this case, and the technology of adjusting the content of water using methods such as azeotropic distillation is a common knowledge in the concerned art (refer to Exhibit A-6~Exhibit A-8), the above-noted technology construction is no more than a simple supplementary process that anyone who is skilled in the art can easily adopt.

(H) Claim 22, Claim 23, Claim 47, Claim 48, Claim 71 and Claim 72 of the patent invention of this case specify a substituted aniline derivative. However, since there are no differences in the effects depending on the types of substituents, this is merely a simple change in materials. Furthermore, Claim 41, Claim 42, and Claim 66 of the patent invention of this case involve

a reduction procedure and a reductive alkylation procedure, which is a simple addition of a common knowledge in the concerned art.

(I) Then, Claims 2~6, Claims 9~11, Claim 13, Claim 14, Claim 16, Claims 18~23, Claims 25~29, Claim 32, Claim 33, Claim 34, Claim 36, Claim 37, Claim 39, Claims 41~48, Claims 50~54, Claims 57~59, Claim 61, Claim 62, Claim 64, Claims 66~72 of the patent invention of this case are deemed something that can be easily invented by anyone who is skilled in the art from the compared invention.

(J) On the other hand, Claim 7, Claim 8, Claim 12, Claim 15, Claim 17, Claim 30, Claim 31, Claim 35, Claim 38, Claim 40, Claim 55, Claim 56, Claim 60, Claim 63 and Claim 65 of the patent invention of this case select dimethyl sulfoxide, methanol, ammonium derivatives and a base condition as a solvent medium, protic material, a base and the reaction condition respectively. Since these selections are different from the corresponding components of the compared invention, and there are significant effects of improved yields due to these differences, they cannot be regarded as something that can be easily invented by anyone who is skilled in the art from the compared invention.

(4) Claim 73 and Claim 74 of the patent invention of this case

Claim 73 and Claim 74 of the patent invention of this case involve diammonium salt; as diammonium salt is a new compound that is not described in the compared invention and has a different chemical structure and usage compared to p-NDPA that is described in the compared invention, [these claims] cannot be deemed something that can be easily invented by anyone who is skilled in the art from the compared invention.

C. Sub-Conclusion

As have been examined so far, Claim 7, Claim 8, Claim 12, Claim15, Claim 17, Claim 30, Claim 31, Claim 35, Claim 38, Claim 40, Claim 55, Claim 56, Claim 60, Claim 63, and Claim 65 of the patent invention of this case show differences in some parts of their construction as compared to the compared invention, and improvement in the yield is significant

due to such differences in the construction and thus they are deemed something that cannot be easily invented by anyone who is skilled in the art. Therefore, the argument of the Complainant that the registration of these Claims should be invalidated cannot be accepted. However, since the rest of the Claims of the patent invention of this case can be easily invented by anyone who is skilled in the art, the argument of the Complainant that finds fault with those parts is justifiable. Although there are other points that the concerned parties argue about, since they are not going to affect the conclusion of the decision on this case, descriptions of such argument shall be omitted.

6. Conclusion

Therefore, it is the decision of this court that a portion of the petition for ruling of this case shall be cited, and pursuant to the principle that a party defeated shall bear the court costs associated, of the costs of trial & ruling, the Respondent shall bear the portion relating to 57/74 and the Complainant shall bear the portion relating to 17/74. As such, this court rules as indicated in the holdings.

September 30, 2005

Chief Judge Judge Yoon Won Lee
[seal:] Judge Yoon Won Lee
Judge Min Ho Gong
[seal:] Judge Min Ho Gong
Judge Yeo Hyeon Hwang
[seal:] Judge Yeo Hyeon Hwang

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内 容 简 介

本书依据经典有机合成反应的应用和进展，收入生产、教学、科研常用的1700余种有机化合物，按反应类型分章编写。对于每一种有机化合物，介绍品名、化学文摘登记号、英文名、别名、分子式、相对分子质量、理化性质、合成反应、操作步骤和参考文献等内容。理化性质尽量引用最新资料记载的数据，操作步骤的资料较为详实可靠，书后附有分子式索引，全书图文采用电脑编排。

本书实用性强，可供从事医药、农药、染料、颜料、日化、助剂、试剂等有关化学、化工行业的生产、科研、教学、实验室工作者及大专学生、研究生使用。

有机合成事典
吴毓廷 编著
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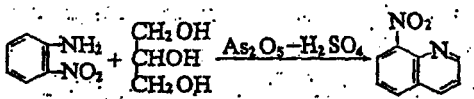
8－硝基喹啉　　[607-35-2]

8－Nitroquinoline

分子式　$C_9H_6N_2O_2$　　相对分子质量　174.16

理化性质　无色单斜结晶．熔点 89～91 ℃．微溶于冷水，溶于乙醇、乙醚和苯．

合成反应



操作步骤　向配有机械搅拌器、温度计和回流冷凝器的 500 mL 三口烧瓶中，加入 69 g(0.5 mol)邻硝基苯胺、86 g(0.375 mol)五氧化二砷和 184 g(2 mol)甘油．开动搅拌，用油浴加热至 100 ℃，从冷凝器上口滴入 220 g(120 mL)浓硫酸，加入速度使反应温度不高于 120 ℃．加完后升温至 130～135 ℃，继续搅拌 7～8 h．冷却后，倒入 1500 mL 水中．加入 15 g 活性炭，在 90 ℃ 保温搅拌 1 h．过滤，滤液冷却后，用稀氨水(1∶1)中和，滤出粗品，水洗．用热水或甲醇重结晶，得产品 8－硝基喹啉 45 g，产率 52%．

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[1] Vogel Arthur. Textbook of Practical Organic Chemistry. 4th ed. London: Longman Group Limited, 1978. 91

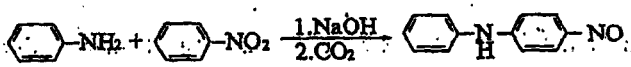
对亚硝基二苯胺　　[156-10-5]

4－Nitrosodiphenylamine

分子式　$C_{12}H_{10}N_2O$　　相对分子质量　198.23

理化性质　绿色晶体．熔点 144 ℃(分解)．易溶于乙醇、乙醚、氯仿．

合成反应



操作步骤　向烧瓶中加入 30 g 苯胺、30 g 硝基苯和 120 g 研细并彻底干燥的氢氧化钠，混匀后在油浴上加热至 110～120 ℃，经短期搅拌后，混合物变成稀薄的液体．将温度升至 120～125 ℃，反应液颜色变深并浓稠，当反应液固化时，反应即告完成．

冷却后，将反应物溶于 1 L 热水，然后在冰浴中冷却至碱及偶氮苯晶体析出．过滤．滤液通二氧化碳 2 h，滤出蓝黑色针状晶体．滤液再通二氧化碳 2 h，滤取第二批产物．两批产物合并，用乙醇重结晶，得纯净的对亚硝基二苯胺．

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[1] Windholz Martha ed. The Merck Index. 11th ed. Rahway (New Jersey): Merck & Co., Inc., 1988. 6560

[2] Welcher F J. Organic Analytical Reagents, Ⅲ. New York: D Van Nostrand Co, 1947. 408

[3] (日) 化学工业日报社．11290 の化学商品．东京：化学工业日报社，1990. 938

Yoe[6] reports that this method has been found to be valueless, and he does not recommend it for the determination of perchlorates.

1. A. Baeyer and H. Caro, *Ber.* 7, 810, 963 (1874).
2. L. G. Overholser and J. H. Yoe, *J. Am. Chem. Soc.* 63, 3224-29 (1941); *C.A.* 36, 363 (1942).
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5. A. Monnier, *Arch. sci. phys. nat.* 42, 210 (1916).
6. J. H. Yoe, *Photometric Chemical Analysis*, Vol. I, p. 164, John Wiley, New York.

p-NITROSODIPHENYLAMINE Synonym: Phenylamino-*p*-nitrosobenzene

$C_{12}H_{10}ON_2$ Mol. Wt. 198.22 Beil. Ref. XII, 207(294).

$$C_6H_5—NH—C_6H_4NO$$

Use: Detection and determination of palladium.

p-Nitrosodiphenylamine is obtained as a green crystalline solid from benzene. It melts at 143° C. It is easily soluble in alcohol, ether and chloroform.

Preparation: Mix 30 g. of aniline, 30 g. of nitrobenzene and 120 g. of finely powdered, completely dry sodium hydroxide in a flask and heat in an oil-bath to 110-120° C. Stir frequently. After a short time the mixture is transformed into a thin liquid. If the temperature rises to 120-125° C. the liquid becomes darker and thicker. When the mass has solidified, the reaction is complete. Cool and dissolve in about 1 liter of hot water. Warm the mixture on a water-bath and allow to cool in an ice mixture until the base and azobenzene are crystallized. Filter with suction and wash several times with water to remove the alkali. Treat the strongly alkaline liquid with carbon dioxide and after about 2 hours filter off the bluish-black needles which separate. Treat the filtrate an additional 2 hours with carbon dioxide and collect a second crop of crystals. Add these to the first, and then purify by crystallizing from alcohol.[1]

Detection and determination of palladium. *p*-Nitrosodiphenylamine reacts with palladous chloride in a neutral or slightly acid solution to form either a deep red solution or a purplish-brown precipitate. As little as 0.005γ of palladium can be detected with this reagent by means of a spot plate test. The only other metallic ions which form colored compounds with this reagent are silver and gold, but the reactions with these metals are much less sensitive. Oxidizing agents interfere with the reaction, and cyanides and iodides prevent the formation of the colored compound. Precipitation is quantitative if an excess of the reagent is added to a slightly acid solution of a palladous salt. The compound appears to be $Pd[C_6H_5NHC_6H_4NO]_2Cl_2$.[2-4]

Small quantities of palladium may be determined colorimetrically by means of the color which appears when solutions of palladous salts are treated with *p*-nitrosodiphenylamine. *p*-Nitrosodiphenylamine appears to be superior to *p*-nitrosodimethylaniline for the palladium determination, since with the former a higher concentration of iron, copper and gold is permissible. The reagent cannot be used in solutions containing high concentrations of neutral salts, since, for example, the determination fails if the concentration of sodium chloride exceeds 0.03 M. The following procedure may be used for the colorimetric determination of palladium in the presence of gold:[5]

Reagents. ***p*-Nitrosodiphenylamine reagent:** Dissolve 50 mg. of p-nitrosodiphenylamine in 500 ml. of 95 per cent ethyl alcohol and dilute to 1 liter.

Buffer solution: Add 240 ml. of 1 N hydrochloric acid to 200 ml. of 1 N sodium acetate solution and dilute to 1 liter.

Procedure. Add sufficient hydrochloric acid to 15 ml. or less of the palladium solution to make the concentration of the acid about 10 per cent. Transfer to a small separatory funnel, add 10 ml. of ethyl acetate or ethyl ether, shake, and drain off the acid solution. This treatment serves to remove most of the gold, which remains in the upper layer. Shake the ethyl acetate or ether layer with a little 10 per cent hydrochloric acid and again separate. If necessary repeat the treatment with ethyl acetate or ether. Evaporate the aqueous solution just to dryness, take up in a little hydrochloric acid and again evaporate nearly to dryness. Dissolve the residue in a little water, add 25 ml. of the buffer solution and 2 ml. of the reagent solution, and dilute to 100 ml. with water. Let stand 30 minutes and compare the resulting color with that obtained similarly with solutions containing known quantities of palladium, which should range from 0.5 to 50γ.

Since silver interferes with the determination of palladous chloride, palladous nitrate is determined in the presence of a nitric acid-sodium acetate buffer of pH 1.2.

Reagent. Dissolve 25 mg. of *p*-nitrosodiphenylamine in 50 ml. of ethyl alcohol and dilute to 100 ml. with water. Filter if any of the solid remains undissolved.

Procedure. Pipet 25 ml. of a sodium acetate-nitric acid buffer of pH 1.2 into a 100-ml. volumetric flask. Add the palladous nitrate solution, and 2 ml. of *p*-nitrosodiphenylamine reagent, and then dilute to the mark with water. Mix thoroughly and allow to stand for 20-30 minutes before making the color comparison. The color develops in about 30 minutes and is stable for 1-2 hours.

1. A. Wohl, *Ber.* 36, 4135 (1903).
2. L. G. Overholser and J. H. Yoe, *J. Am. Chem. Soc.* 63, 3224-29 (1941); *C.A.* 36, 363 (1942).
3. J. H. Yoe and L. G. Overholser, *J. Am. Chem. Soc.* 61, 2058-63 (1939); *C.A.* 33, 7691 (1939).
4. L. G. Overholser and J. H. Yoe, *Va. J. Sci.* 1, 162-7 (1940).

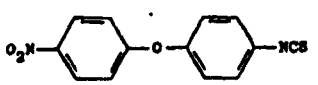
α-NITROSO-*β*-NAPHTHYLAMINE

$C_{10}H_8ON_2$ Mol. Wt. 172.18 Beil. Ref. VII, 717.

$$C_{10}H_6(NO)NH_2 \rightleftharpoons C_{10}H_6(=NH)=NOH$$

Use: Determination of cobalt, copper and nickel.

1,491,477 (1967 to Agripat), *C.A.* 69, 76923y (1968); Martvon, Antos, *Chem. Zvesti* 23, 181 (1969); Antos *et al.*, Ger. pat. 1,932,690 (1970 to Ceskoslovenska Akademie Ved), *C.A.* 72, 100265v (1970). Activity in dogs: Gemmell, Oudemans, *Res. Vet. Sci.* 19, 217 (1975).



Crystals, mp 107-113°, Martvon, Antos, *loc. cit.*; 124-125°, Fr. pat. 1,491,477. Insol in water; sol in organic solvents.
THERAP CAT (VET): Anthelmintic.

6556. *N*-Nitrosodiethanolamine. *2,2'-(Nitrosoimino)-bisethanol; 2,2'-nitrosiminodiethanol;* di-(2-hydroxyethyl)-nitrosamine; NDELA. $C_4H_{10}N_2O_3$; mol wt 134.13. C 35.82%, H 7.51%, N 20.88%, O 35.79%. $(HOCH_2CH_2)_2NNO$. Formed by the action of nitrites on di- or triethanolamine. Prepn: E. R. H. Jones, W. Wilson, *J. Chem. Soc.* 1949, 547; R. Preussmann, *Ber.* 98, 1571 (1962); W. Lijinsky *et al., J. Nat. Cancer Inst.* 49, 1239 (1972). Carcinogenicity study: H. Druckery *et al., Z. Krebsforsch.* 69, 103 (1967). Impurity in cutting fluids: T. Y. Fan *et al., Science* 196, 70 (1977); in cosmetics: *eidem, Food Cosmet. Toxicol.* 15, 423 (1977). Mutagenicity study: A. Hesbert *et al., Mutat. Res.* 68, 207 (1979).

Light yellow oil, $bp_{0.01}$ 125°. n_D^{20} 1.4849.

Note: This substance may reasonably be anticipated to be a carcinogen: *Fourth Annual Report on Carcinogens* (NTP 85-002, 1985) p 148.

6557. *N*-Nitrosodiethylamine. *N-Ethyl-N-nitrosoethanamine; diethylnitrosamine;* DEN; DENA; NDEA. $C_4H_{10}N_2O$; mol wt 102.14. C 47.04%, H 9.87%, N 27.43%, O 15.66%. $(C_2H_5)_2NNO$. Detected in trace amounts in tobacco smoke: Druckney, Preussman, *Naturwiss.* 49, 498 (1962) and in various processed foods: Hedler, Marquardt, *Food Cosmet. Toxicol.* 6, 341 (1968); Friemuth, Glasser, *Nahrung* 14, 357 (1970). Formed by the interaction of nitrite with diethylamine and by the action of nitrate-reducing bacteria. Industrial prepn: Reilly, Ger. pat. 1,085,166 (1960 to du Pont), *C.A.* 56, 4594h (1962); Levering, Maury, U.S. pat. 3,090,786 (1963 to Hercules Powder); Miniaci, Galli, *Chim. Ind. (Milan)* 46, 173 (1964). Hepatotoxicity and carcinogenicity studies: Schmaehl *et al., Naturwiss.* 54, 341 (1967); Grover, Fischer, *Eur. J. Cancer* 7, 77 (1971); Badar *et al., Arch. Geschwulstforsch.* 37, 327 (1971). General review: Magee, Barnes, *Adv. Cancer Res.* 10, 163-246 (1967).

Slightly yellow liq. d_4^{20} 0.9422. bp 175-177°. bp_9 47°. n_D^{20} 1.4388. Sol in water, alc, ether.

Note: This substance may reasonably be anticipated to be a carcinogen: *Fourth Annual Report on Carcinogens* (NTP 85-002, 1985) p 149.

USE: Gasoline and lubricant additive; antioxidant; stabilizer.

6558. *N*-Nitrosodimethylamine. *N-Methyl-N-nitrosomethanamine;* dimethylnitrosamine; DMN; DMNA. $C_2H_6N_2O$; mol wt 74.08. C 32.42%, H 8.16%, N 37.82%, O 21.60%. $(CH_3)_2NNO$. Reportedly found in trace amounts in tobacco smoke condensates: Rhoades, Johnson, *Nature* 236, 307 (1972); in cured meat products, notably bacon: Sen *et al., ibid.* 241, 473 (1973); in smoked and salted fish: Fazio *et al., J. Agr. Food Chem.* 19, 250 (1971); Fong, Chan, *Nature* 243, 421 (1973). Formed by the interaction of nitrite with dimethylamine and by the action of nitrate-reducing bacteria. Industrial prepn: Brit. pat. 772,331 (1957 to Olin Mathieson), *C.A.* 51, 14783a (1957); Ioffe, *Zh. Obshch. Khim.* 28, 1296 (1958); Norris, *J. Am. Chem. Soc.* 81, 3346 (1959); Campbell, U.S. pat. 2,981,752 (1961 to C.S.C.); Datin, Elliott, U.S. pat. 3,136,821 (1964 to Allied Chem.). Metabolism and toxicity: Magee, Vandekar; Magee, *Biochem. J.* 70, 600, 606 (1958); Heath, *ibid.* 85, 72 (1962). Carcinogenicity studies: Magee, Barnes, *Brit J. Cancer* 10, 114 (1956); *see also eidem, Adv. Cancer Res.* 10, 163-246 (1967). Chemistry: Layne *et al., J. Am. Chem. Soc.* 85, 435, 1816 (1963).

Yellow liquid. bp 151-153°. bp_{40} 67.1°. d_4^{20} 1.0048. n_D^{20} 1.4368. Very sol in water, alcohol, ether. LD_{50} i.p. in rats: 34 mg/kg (Heath).

Note: This substance may reasonably be anticipated to be a carcinogen: *Fourth Annual Report on Carcinogens* (NTP 85-002, 1985) p 151.

USE: Formerly in the prodn of rocket fuels; antioxidant; additive for lubricants; softener of copolymers.

6559. *p*-Nitroso-*N,N*-dimethylaniline. *N,N-Dimethyl-4-nitrosobenzenamine;* Accelerine. $C_8H_{10}N_2O$; mol wt 150.18. C 63.98%, H 6.71%, N 18.66%, O 10.65%. Prepd in the cold from $NaNO_2$ and a soln of dimethylaniline in HCl.

Green plates or leaflets. mp 92.5-93.5°; also stated as 87-88°. Volatile with steam. Insol in water; sol in alcohol, ether.

USE: Manuf organic compds; accelerator in vulcanizing; in printing fabrics.

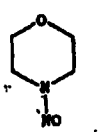
6560. *p*-Nitrosodiphenylamine. *4-Nitroso-N-phenylbenzenamine.* $C_{12}H_{10}N_2O$; mol wt 198.22. C 72.71%, H 5.09%, N 14.13%, O 8.07%. $C_6H_5NHC_6H_4NO$.

Green plates with bluish luster (from benzene) or steel-blue prisms or plates (from ether + water). mp 144-145°. Slightly sol in water or petr ether; freely sol in alcohol, ether, chloroform, benzene. Dissolves in H_2SO_4 with a red color, which suddenly changes to violet on warming.

Note: This substance may reasonably be anticipated to be a carcinogen: *Fourth Annual Report on Carcinogens* (NTP 85-002, 1985) p 152.

USE: Accelerator in vulcanizing rubber.

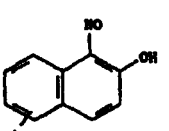
6561. *N*-Nitrosomorpholine. *4-Nitrosomorpholine;* NMOR. $C_4H_8N_2O_2$; mol wt 116.11. C 41.37%, H 6.94%, N 24.12%, O 27.56%. Prepn: L. Knorr, *Ann.* 301, 1 (1898); F. Chapman, *J. Chem. Soc.* 1949, 1631; G. Olah *et al., Ber.* 89, 2374 (1956). Carcinogenicity studies: H. Druckrey *et al., Naturwiss.* 48, 134 (1961); P. Bannasch, H.-A. Müller, *Arzneimittel-Forsch.* 14, 805 (1964); *IARC Monographs* 17, 263 (1978). Metabolism: B. W. Stewart, P. N. Magee, *Biochem. J.* 126, 21P (1972).



Yellow crystals, mp 29°. bp_{28} 139-140°; bp_{747} 224-224.5°. Sol in water. LD_{50} orally in rats: 282 mg/kg (Druckrey).

Note: This substance may reasonably be anticipated to be a carcinogen: *Fourth Annual Report on Carcinogens* (NTP 85-002, 1985) p 157.

6562. 1-Nitroso-2-naphthol. *1-Nitroso-2-naphthalenol;* nitroso-β-naphthol. $C_{10}H_7NO_2$; mol wt 173.16. C 69.36%, H 4.07%, N 8.09%, O 18.48%. Prepared by the addition of H_2SO_4 to a mixture of β-naphthol dissolved in aq NaOH and $NaNO_2$: C. S. Marvel, P. K. Porter, *Org. Syn.* coll. vol. I, 411 (2nd ed., 1941).



Yellowish-brown needles from petr ether, mp 109-110°. Sol in 1000 parts water, 35 parts alcohol; also sol in hot alcohol, benzene, ether, carbon disulfide, caustic alkali solns, glacial acetic acid; slightly sol in cold petr ether.

USE: To prevent gum formation in gasoline; in analytical chemistry in the determination of cobalt (to separate it from nickel).

6563. 4-Nitrosophenol. Quinone oxime; quinone monoxime. $C_6H_5NO_2$; mol wt 123.11. C 58.53%, H 4.09%, N 11.38%, O 25.99%.

Manual of Organic Synthesis

Editor: Fan Neng-ting

Beijing Institute of Technology Press

(Beijing) New Registration No. 149

Summary of Contents

This book traces the development and application of classical organic synthetic reactions, collects entries for over 1700 organic compounds that are commonly used in manufacturing, teaching, and research, and is organized into chapters for each reaction type. For each organic compound, we include its chemical name, Chemical Abstract registration number, English name, other name(s), molecular formula, relative molecular mass, physical and chemical properties, synthesis and reaction steps therefor, and references. We strive to cite data in the most current references for the physical and chemical properties. Information on the reaction steps for these chemical compounds' synthesis is reliable. The book contains an index of molecular formula. The text and graphs in this book are typeset with computer.

This book has high applicability and is suitable for use by professionals and college and graduate students in the manufacturing, research, teaching and laboratory work in the areas of pharmaceutical, agricultural chemical, dyestuff, pigments, consumer-use chemicals, additives, and chemical reagents industries.

Manual of Organic Synthesis

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SCS014061

8-Nitroquinoline

(Translation for this entry is omitted)

4-Nitrosodiphenylamine [156-10-5]

Molecular formula C12H10H2O **Relative molecular weight** 198.23

Physical and chemical properties Green crystal, melting point 144 °C (decomposition), soluble in ethanol. ether, chloroform.

Synthetic reaction (see original)

Aniline + Nitrobenzene —(1. NaOH; 2. CO2)→ 4-nitrosodiphenylamine

Reaction steps Mix 30 gram of aniline, 30 gram of nitrobenzene and 120 gram of finely powdered, completely dry sodium hydroxide in a flask and heat in an oil-bath to 110-120 °C. Stir for a short time and the mixture is transformed into a thin liquid. Raise the temperature to 120-125 °C, the liquid becomes darker and thicker. When the mass has solidified, the reaction is complete.

Cool and dissolve in about 1 liter of hot water. Then cool in an ice mixture until the base and azobenzene are crystallized. Filter and the filtrate is treated with carbon dioxide for 2h, and filter off the bluish-black needle crystals. Treat the filtrate an additional 2h with carbon dioxide and collect a second crop of crystals. Combine these two crops and then purify by crystallizing from alcohol to get pure 4-nitrosodiphenylamine.

References

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Preparation: Mix 30 g. of aniline, 30 g. of nitrobenzene and 120 g. of finely powdered, completely dry sodium hydroxide in a flask and heat in an oil-bath to 110-120° C. Stir frequently. After a short time the mixture is transformed into a thin liquid. If the temperature rises to 120-125° C. the liquid becomes darker and thicker. When the mass has solidified, the reaction is complete. Cool and dissolve in about 1 liter of hot water. Warm the mixture on a water-bath and allow to cool in an ice mixture until the base and azobenzene are crystallized. Filter with suction and wash several times with water to remove the alkali. Treat the strongly alkaline liquid with carbon dioxide and after about 2 hours filter off the bluish-black needles which separate. Treat the filtrate an additional 2 hours with carbon dioxide and collect a second crop of crystals. Add these to the first, and then purify by crystallizing from alcohol.[1]

Detection and determination of palladium. *p*-Nitrosodiphenylamine reacts with palladous chloride in a neutral or slightly acid solution to form either a deep red solution or a purplish-brown precipitate. As little as 0.005γ of palladium can be detected with this reagent by means of a spot plate test. The only other metallic ions which form colored compounds with this reagent are silver and gold, but the reactions with these metals are much less sensitive. Oxidizing agents interfere with the reaction, and cyanides and iodides prevent the formation of the colored compound. Precipitation is quantitative if an excess of the reagent is added to a slightly acid solution of a palladous salt. The compound appears to be $Pd[C_6H_5NHC_6H_4NO]_2Cl_2$.[2-4]

Small quantities of palladium may be determined colorimetrically by means of the color which appears when solutions of palladous salts are treated with *p*-nitrosodiphenylamine. *p*-Nitrosodiphenylamine appears to be superior to *p*-nitrosodimethylaniline for the palladium determination, since with the former a higher concentration of iron, copper and gold is permissible. The reagent cannot be used in solutions containing high concentrations of neutral salts, since, for example, the determination fails if the concentration of sodium chloride exceeds 0.03 M. The following procedure may be used for the colorimetric determination of palladium in the presence of gold:[5]

Reagents. *p-Nitrosodiphenylamine reagent:* Dissolve 50 mg. of p-nitrosodiphenylamine in 500 ml. of 95 per cent ethyl alcohol and dilute to 1 liter.

Buffer solution: Add 240 ml. of 1 N hydrochloric acid to 200 ml. of 1 N sodium acetate solution and dilute to 1 liter.

Procedure. Add sufficient hydrochloric acid to 15 ml. or less of the palladium solution to make the concentration of the acid about 10 per cent. Transfer to a small separatory funnel, add 10 ml. of ethyl acetate or ethyl ether, shake, and drain off the acid solution. This treatment serves to remove most of the gold, which remains in the upper layer. Shake the ethyl acetate or ether layer with a little 10 per cent hydrochloric acid and again separate. If necessary repeat the treatment with ethyl acetate or ether. Evaporate the aqueous solution just to dryness, take up in a little hydrochloric acid and again evaporate nearly to dryness. Dissolve the residue in a little water, add 25 ml. of the buffer solution and 2 ml. of the reagent solution, and dilute to 100 ml. with water. Let stand 30 minutes and compare the resulting color with that obtained similarly with solutions containing known quantities of palladium, which should range from 0.5 to 50γ.

Since silver interferes with the determination of palladous chloride, palladous nitrate is determined in the presence of a nitric acid-sodium acetate buffer of pH 1.2.

Reagent. Dissolve 25 mg. of *p*-nitrosodiphenylamine in 50 ml. of ethyl alcohol and dilute to 100 ml. with water. Filter if any of the solid remains undissolved.

Procedure. Pipet 25 ml. of a sodium acetate-nitric acid buffer of pH 1.2 into a 100-ml. volumetric flask. Add the palladous nitrate solution, and 2 ml. of *p*-nitrosodiphenylamine reagent, and then dilute to the mark with water. Mix thoroughly and allow to stand for 20-30 minutes before making the color comparison. The color develops in about 30 minutes and is stable for 1-2 hours.

1. A. Wohl, *Ber.* 36, 4135 (1903).
2. L. G. Overholser and J. H. Yoe, *J. Am. Chem. Soc.* 63, 3224-29 (1941); *C.A.* 36, 363 (1942).
3. J. H. Yoe and L. G. Overholser, *J. Am. Chem. Soc.* 61, 2058-63 (1939); *C.A.* 33, 7691 (1939).
4. L. G. Overholser and J. H. Yoe, *Va. J. Sci.* 1, 162-7 (1940).

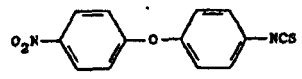
α-NITROSO-*β*-NAPHTHYLAMINE

$C_{10}H_8ON_2$ Mol. Wt. 172.18 Beil. Ref. VII, 717.

$$C_{10}H_6(NO)NH_2 \rightleftarrows C_{10}H_6(=NH)=NOH$$

Use: Determination of cobalt, copper and nickel.

1,491,477 (1967 to Agripat), *C.A.* 69, 76923y (1968); Martvon, Antos, *Chem. Zvesti* 23, 181 (1969); Antos *et al.*, Ger. pat. 1,932,690 (1970 to Ceskoslovenska Akademie Ved), *C.A.* 72, 100265v (1970). Activity in dogs: Gemmell, Oudemans, *Res. Vet. Sci.* 19, 217 (1975).



Crystals, mp 107-113°, Martvon, Antos, *loc. cit.*; 124-125°, Fr. pat. 1,491,477. Insol in water; sol in organic solvents.

THERAP CAT (VET): Anthelmintic.

6556. *N*-Nitrosodiethanolamine. *2,2'-(Nitrosoimino)-bisethanol; 2,2'-nitrosiminodiethanol;* di-(2-hydroxyethyl)-nitrosamine; NDELA. $C_4H_{10}N_2O_3$; mol wt 134.13. C 35.82%, H 7.51%, N 20.88%, O 35.79%. $(HOCH_2CH_2)_2NNO$. Formed by the action of nitrites on di- or triethanolamine. Prepn: E. R. H. Jones, W. Wilson, *J. Chem. Soc.* 1949, 547; R. Preussmann, *Ber.* 95, 1571 (1962); W. Lijinsky *et al.*, *J. Nat. Cancer Inst.* 49, 1239 (1972). Carcinogenicity study: H. Druckery *et al.*, *Z. Krebsforsch.* 69, 103 (1967). Impurity in cutting fluids: T. Y. Fan *et al.*, *Science* 196, 70 (1977); in cosmetics: *eidem, Food Cosmet. Toxicol.* 15, 423 (1977). Mutagenicity study: A. Hesbert *et al.*, *Mutat. Res.* 68, 207 (1979).

Light yellow oil, $bp_{0.8}$ 125°. n_D^{20} 1.4849.

Note: This substance may reasonably be anticipated to be a carcinogen: *Fourth Annual Report on Carcinogens* (NTP 85-002, 1985) p 148.

6557. *N*-Nitrosodiethylamine. *N-Ethyl-N-nitrosoethanamine;* diethylnitrosamine; DEN; DENA; NDEA. $C_4H_{10}N_2O$; mol wt 102.14. C 47.04%, H 9.87%, N 27.43%, O 15.66%. $(C_2H_5)_2NNO$. Detected in trace amounts in tobacco smoke: Druckney, Preussman, *Naturwiss.* 49, 498 (1962) and in various processed foods: Hedler, Marquardt, *Food Cosmet. Toxicol.* 6, 341 (1968); Friemuth, Glaeser, *Nahrung* 14, 357 (1970). Formed by the interaction of nitrite with diethylamine and by the action of nitrate-reducing bacteria. Industrial prepn: Reilly, Ger. pat. 1,085,166 (1960 to du Pont), *C.A.* 56, 4594h (1962); Levering, Maury, U.S. pat. 3,090,786 (1963 to Hercules Powder); Minisci, Galli, *Chim. Ind. (Milan)* 46, 173 (1964). Hepatotoxicity and carcinogenicity studies: Schmaehl *et al.*, *Naturwiss.* 54, 341 (1967); Grover, Fischer, *Eur. J. Cancer* 7, 77 (1971); Bader *et al.*, *Arch. Geschwulstforsch.* 37, 327 (1971). General review: Magee, Barnes, *Adv. Cancer Res.* 10, 163-246 (1967).

Slightly yellow liq. d_4^{20} 0.9422. bp 175-177°. bp_9 47°. n_D^{20} 1.4388. Sol in water, alc, ether.

Note: This substance may reasonably be anticipated to be a carcinogen: *Fourth Annual Report on Carcinogens* (NTP 85-002, 1985) p 149.

USE: Gasoline and lubricant additive; antioxidant; stabilizer.

6558. *N*-Nitrosodimethylamine. *N-Methyl-N-nitrosomethanamine;* dimethylnitrosamine; DMN; DMNA. $C_2H_6N_2O$; mol wt 74.08. C 32.42%, H 8.16%, N 37.82%, O 21.60%. $(CH_3)_2NNO$. Reportedly found in trace amounts in tobacco smoke condensates: Rhoades, Johnson, *Nature* 236, 307 (1972); in cured meat products, notably bacon: Sen *et al.*, *Ibid.* 241, 473 (1973); in smoked and salted fish: Fazio *et al.*, *J. Agr. Food Chem.* 19, 250 (1971); Fong, Chan, *Nature* 243, 421 (1973). Formed by the interaction of nitrite with dimethylamine and by the action of nitrate-reducing bacteria. Industrial prepn: Brit. pat. 772,331 (1957 to Olin Mathieson), *C.A.* 51, 14783a (1957); Ioffe, *Zh. Obshch. Khim.* 28, 1296 (1958); Norris, *J. Am. Chem. Soc.* 81, 3346 (1959); Campbell, U.S. pat. 2,981,752 (1961 to C.S.C.); Datin, Elliott, U.S. pat. 3,136,821 (1964 to Allied Chem.). Metabolism and toxicity: Magee, Vandekar; Magee, *Biochem. J.* 70, 600, 606 (1958); Heath, *Ibid.* 85, 72 (1962). Carcinogenicity studies: Magee, Barnes, *Brit J. Cancer* 10, 114 (1956); *see also eidem, Adv. Cancer Res.* 10, 163-246 (1967). Chemistry: Layne *et al.*, *J. Am. Chem. Soc.* 85, 435, 1816 (1963).

Yellow liquid. bp 151-153°. bp_{40} 67.1°. d_4^{20} 1.0048. n_D^{20} 1.4368. Very sol in water, alcohol, ether. LD_{50} i.p. in rats: 34 mg/kg (Heath).

Note: This substance may reasonably be anticipated to be a carcinogen: *Fourth Annual Report on Carcinogens* (NTP 85-002, 1985) p 151.

USE: Formerly in the prodn of rocket fuels; antioxidant; additive for lubricants; softener of copolymers.

6559. *p*-Nitroso-*N,N*-dimethylaniline. *N,N-Dimethyl-4-nitrosobenzenamine;* Accelerine. $C_8H_{10}N_2O$; mol wt 150.18. C 63.98%, H 6.71%, N 18.66%, O 10.65%. Prepd in the cold from $NaNO_2$ and a soln of dimethylaniline in HCl.

Green plates or leaflets. mp 92.5-93.5°; also stated as 87-88°. Volatile with steam. Insol in water; sol in alcohol, ether.

USE: Manuf organic compds; accelerator in vulcanizing; in printing fabrics.

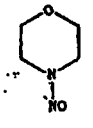
6560. *p*-Nitrosodiphenylamine. *4-Nitroso-N-phenylbenzenamine.* $C_{12}H_{10}N_2O$; mol wt 198.22. C 72.71%, H 5.09%, N 14.13%, O 8.07%. $C_6H_5NHC_6H_4NO$.

Green plates with bluish luster (from benzene) or steel-blue prisms or plates (from ether + water). mp 144-145°. Slightly sol in water or petr ether; freely sol in alcohol, ether, chloroform, benzene. Dissolves in H_2SO_4 with a red color, which suddenly changes to violet on warming.

Note: This substance may reasonably be anticipated to be a carcinogen: *Fourth Annual Report on Carcinogens* (NTP 85-002, 1985) p 152.

USE: Accelerator in vulcanizing rubber.

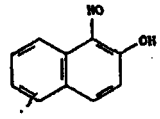
6561. *N*-Nitrosomorpholine. *4-Nitrosomorpholine;* NMOR. $C_4H_8N_2O_2$; mol wt 116.11. C 41.37%, H 6.94%, N 24.12%, O 27.56%. Prepn: L. Knorr, *Ann.* 301, 1 (1898); F. Chapman, *J. Chem. Soc.* 1949, 1631; G. Oláh *et al.*, *Ber.* 89, 2374 (1956). Carcinogenicity studies: H. Druckrey *et al.*, *Naturwiss.* 48, 134 (1961); P. Bannasch, H.-A. Müller, *Arzneimittel-Forsch.* 14, 805 (1964); *IARC Monographs* 17, 263 (1978). Metabolism: B. W. Stewart, P. N. Magee, *Biochem. J.* 126, 21P (1972).



Yellow crystals, mp 29°. bp_{25} 139-140°; bp_{747} 224-224.5°. Sol in water. LD_{50} orally in rats: 282 mg/kg (Druckrey).

Note: This substance may reasonably be anticipated to be a carcinogen: *Fourth Annual Report on Carcinogens* (NTP 85-002, 1985) p 157.

6562. 1-Nitroso-2-naphthol. *1-Nitroso-2-naphthalenol;* nitroso-β-naphthol. $C_{10}H_7NO_2$; mol wt 173.16. C 69.36%, H 4.07%, N 8.09%, O 18.48%. Prepared by the addition of H_2SO_4 to a mixture of β-naphthol dissolved in aq NaOH and $NaNO_2$: C. S. Marvel, P. K. Porter, *Org. Syn.* coll. vol. I, 411 (2nd ed., 1941).



Yellowish-brown needles from petr ether, mp 109-110°. Sol in 1000 parts water, 35 parts alcohol; also sol in hot alcohol, benzene, ether, carbon disulfide, caustic alkali solns, glacial acetic acid; slightly sol in cold petr ether.

USE: To prevent gum formation in gasoline; in analytical chemistry in the determination of cobalt (to separate it from nickel).

6563. 4-Nitrosophenol. Quinone oxime; quinone monoxime. $C_6H_5NO_2$; mol wt 123.11. C 58.53%, H 4.09%, N 11.38%, O 25.99%.

Organic Analytical Reagents

BY

FRANK J. WELCHER, PH.D.
Associate Professor of Chemistry, Indiana University Extension Division

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CHAPTER XIV

NITROSO AMINES

A study of aromatic amines reveals that compounds containing the *p*-nitrosophenyl amino group, *p*-NO—C_6H_4—N=, such as *p*-nitrosoaniline, *p*-nitrosodimethylaniline,[1] *p*-nitrosodiethylaniline and *p*-nitrosodiphenylamine [2] form colored complexes with divalent palladium salts. These compounds are all of the same general type, and are typified by palladous dichlorodiammine, $Pd(NH_3)_2Cl_2$.

Numerous amines yield complexes with palladous chloride but generally the product is yellow colored; thus, aniline [3] and *p*-nitroaniline [4] give yellow complexes with palladous chloride. In contrast, the palladium complexes of the above nitrosoamines are purplish-brown, dark-brown and bright red in color. Diethylaniline, dimethylaniline, *p*-aminophenol, *p*-chloroaniline and *p*-phenylenediamine do not give highly colored complexes with palladium salts. This appears to indicate that the nitroso group must be present to form highly colored complexes, and that the *p*-NO—C_6H_4—N= group is responsible for the characteristic reaction with palladium salts. The presence of the nitroso group is also responsible for more selective reactions for palladium. Thus diphenylamine and its amino or hydroxyl derivatives give highly colored reactions with numerous oxidizing agents, while the nitroso derivative reacts only with strong oxidizing agents. Similarly *p*-aminodiethylaniline reacts with weaker oxidizing agents than does *p*-nitrosodiethylaniline.

1. S. C. Ogburn, *J. Am. Chem. Soc.* 48. 2493 (1926).
2. J. H. Yoe and L. G. Overholser, *J. Am. Chem. Soc.* 61, 2058 (1939).
3. A. Gutbier and A. Krell, *Ber.* 39, 1292 (1906).
4. A. Gutbier and C. Fellner, *Z. anorg. Chem.* 95, 129 (1921).

p-NITROSOANILINE

Synonym: *p*-Quinoneimideoxime

$C_6H_6ON_2$ Mol. Wt. 122.12 Beil. Ref. VII, 625.

NO—C_6H_4—NH_2

Use: Detection and determination of palladium.

p-Nitrosoaniline crystallizes as steel-blue needles. It melts at 173-174° C. It dissolves readily in water with a formation of a green solution.

Preparation: Mix 1 part of nitrosophenol with 5 parts of ammonium chloride and 10 parts of dry ammonium acetate and digest the mass on a water-bath for one-half hour with the addition of a little ammonium carbonate. The mixture turns dark green and dark green crystals of *p*-nitrosoaniline separate on mixing with cold water. Extract the weakly ammoniacal solution with ether to recover more of the compound. To purify, dissolve in hot benzene, heat with animal charcoal, filter, cool and concentrate by evaporating until crystals appear.[1]

Yoe[6] reports that this method has been found to be valueless, and he does not recommend it for the determination of perchlorates.

1. A. Baeyer and H. Caro, *Ber.* 7, 810, 963 (1874).
2. L. G. Overholser and J. H. Yoe, *J. Am. Chem. Soc.* 63, 3224-29 (1941); *C.A.* 36, 363 (1942).
3. L. G. Overholser and J. H. Yoe, *Va. J. Sci.* 1, 162-7 (1940).
4. W. H. J. Vernon and L. Whitby, *J. Soc. Chem. Ind.* 47, 255-8T (1928); *C.A.* 22, 4407 (1928).
5. A. Monnier, *Arch. sci. phys. nat.* 42, 210 (1916).
6. J. H. Yoe, *Photometric Chemical Analysis*, Vol. I, p. 164, John Wiley, New York.

p-NITROSODIPHENYLAMINE Synonym: Phenylamino-*p*-nitrosobenzene

$C_{12}H_{10}ON_2$ Mol. Wt. 198.22 Beil. Ref. XII, 207 (294).

$$C_6H_5—NH—C_6H_4NO$$

Use: Detection and determination of palladium.

p-Nitrosodiphenylamine is obtained as a green crystalline solid from benzene. It melts at 143° C. It is easily soluble in alcohol, ether and chloroform.

Preparation: Mix 30 g. of aniline, 30 g. of nitrobenzene and 120 g. of finely powdered, completely dry sodium hydroxide in a flask and heat in an oil-bath to 110-120° C. Stir frequently. After a short time the mixture is transformed into a thin liquid. If the temperature rises to 120-125° C. the liquid becomes darker and thicker. When the mass has solidified, the reaction is complete. Cool and dissolve in about 1 liter of hot water. Warm the mixture on a water-bath and allow to cool in an ice mixture until the base and azobenzene are crystallized. Filter with suction and wash several times with water to remove the alkali. Treat the strongly alkaline liquid with carbon dioxide and after about 2 hours filter off the bluish-black needles which separate. Treat the filtrate an additional 2 hours with carbon dioxide and collect a second crop of crystals. Add these to the first, and then purify by crystallizing from alcohol.[1]

Detection and determination of palladium. *p*-Nitrosodiphenylamine reacts with palladous chloride in a neutral or slightly acid solution to form either a deep red solution or a purplish-brown precipitate. As little as 0.005γ of palladium can be detected with this reagent by means of a spot plate test. The only other metallic ions which form colored compounds with this reagent are silver and gold, but the reactions with these metals are much less sensitive. Oxidizing agents interfere with the reaction, and cyanides and iodides prevent the formation of the colored compound. Precipitation is quantitative if an excess of the reagent is added to a slightly acid solution of a palladous salt. The compound appears to be $Pd[C_6H_5NHC_6H_4NO]_2Cl_2$.[2-4]

Small quantities of palladium may be determined colorimetrically by means of the color which appears when solutions of palladous salts are treated with *p*-nitrosodiphenylamine. *p*-Nitrosodiphenylamine appears to be superior to *p*-nitrosodimethylaniline for the palladium determination, since with the former a

higher concentration of iron, copper and gold is permissible. The reagent cannot be used in solutions containing high concentrations of neutral salts, since, for example, the determination fails if the concentration of sodium chloride exceeds 0.03 M. The following procedure may be used for the colorimetric determination of palladium in the presence of gold:[3]

Reagents. *p-Nitrosodiphenylamine reagent:* Dissolve 50 mg. of p-nitrosodiphenylamine in 500 ml. of 95 per cent ethyl alcohol and dilute to 1 liter.

Buffer solution: Add 240 ml. of 1 N hydrochloric acid to 200 ml. of 1 N sodium acetate solution and dilute to 1 liter.

Procedure. Add sufficient hydrochloric acid to 15 ml. or less of the palladium solution to make the concentration of the acid about 10 per cent. Transfer to a small separatory funnel, add 10 ml. of ethyl acetate or ethyl ether, shake, and drain off the acid solution. This treatment serves to remove most of the gold, which remains in the upper layer. Shake the ethyl acetate or ether layer with a little 10 per cent hydrochloric acid and again separate. If necessary repeat the treatment with ethyl acetate or ether. Evaporate the aqueous solution just to dryness, take up in a little hydrochloric acid and again evaporate nearly to dryness. Dissolve the residue in a little water, add 25 ml. of the buffer solution and 2 ml. of the reagent solution, and dilute to 100 ml. with water. Let stand 30 minutes and compare the resulting color with that obtained similarly with solutions containing known quantities of palladium, which should range from 0.5 to 50γ.

Since silver interferes with the determination of palladous chloride, palladous nitrate is determined in the presence of a nitric acid-sodium acetate buffer of pH 1.2.

Reagent. Dissolve 25 mg. of *p*-nitrosodiphenylamine in 50 ml. of ethyl alcohol and dilute to 100 ml. with water. Filter if any of the solid remains undissolved.

Procedure. Pipet 25 ml. of a sodium acetate-nitric acid buffer of pH 1.2 into a 100-ml. volumetric flask. Add the palladous nitrate solution, and 2 ml. of *p*-nitrosodiphenylamine reagent, and then dilute to the mark with water. Mix thoroughly and allow to stand for 20-30 minutes before making the color comparison. The color develops in about 30 minutes and is stable for 1-2 hours.

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α-NITROSO-β-NAPHTHYLAMINE

$C_{10}H_8ON_2$ Mol. Wt. 172.18 Beil. Ref. VII, 717.

$$C_{10}H_6(NO)NH_2 \rightleftarrows C_{10}H_6(=NH)=NOH$$

Use: Determination of cobalt, copper and nickel.

H
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v.
TEVA PHARMACEUTICALS USA, INC., a Delaware Corporation, Defendant.
TEVA PHARMACEUTICALS USA, INC., a Delaware corporation, and Teva Pharmaceutical Industries Limited, an Israeli corporation, Counterclaim-Plaintiffs,
v.
Abbott LABORATORIES, an Illinois corporation, Fournier Industrie et Santé, a French corporation, and Laboratories Fournier S.A., a French corporation, Counterclaim-Defendants.
Abbott LABORATORIES, an Illinois corporation, Fournier Industrie et Sante, a French corporation, and Laboratories Fournier S.A., a French corporation, Plaintiffs,
v.
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No. Civ.A. 02-1512-KAJ, Civ.A. 03-120-KAJ.

April 22, 2005.

Mary B. Graham, Morris, Nichols, Arsht & Tunnell, Wilmington, Delaware, for plaintiff Abbott Laboratories. William F. Cavanaugh, Jr., Eugene M. Gelernter, Chad J. Peterman, and Alexis Gander, Patterson, Belknap, Webb Tyler LLP, New York, NY, of counsel.
Frederick L. Cottrell, III, and Anne S. Gaza, Richards, Layton & Finger, Wilmington, Delaware, for plaintiff Fournier Industrie et Santé, and Laboratories Foumier S.A.Charles D. Ossola, and Leslie M. Hill, Arnold and Porter LLP, Washington, District of Columbia, Mark Shanks, Reed Smith LLP, Washington, District of Columbia, Timothy C. Bickham, Steptoe & Johnson LLP, Washington, District of Columbia, of counsel.
Josy W. Ingersoll, and Karen E. Keller, Young Conaway Stargatt & Taylor, LLP, Wilmington, Delaware, for defendant Teva Pharmaceuticals USA, Inc. Bruce M. Gagala, and M. Daniel Hefner, Leydig, Voit & Mayer, Ltd., Chicago, Illinois, of counsel.
Richard K. Herrmann, and Mary B. Materrer, Morris, James, Hitchens & Williams LLP, Wilmington, Delaware, for defendant Impax Laboratories, Inc. Philip J. McCabe, Kenyon & Kenyon, San Jose, California, C. Kyle Musgrove, Kenyon & Kenyon, Washington, District of Columbia, John C. Vetter, Kenyon & Kenyon, New York, NY, of counsel.

MEMORANDUM OPINION

JORDAN, J.

I. INTRODUCTION

***1** This is a patent infringement case. Presently before me are the parties' requests for construction of the disputed claim language of U.S. Patent No. 6,074,670 (issued June 13, 2000) (the " '670 patent"), U.S. Patent No. 6,589,552 B2 (issued July 8, 2003) (the " '552 patent"), U.S. Patent No. 6,277,405 B1 (issued Aug. 21, 2001) (the " '405 patent"), and U.S. Patent No. 6,652,881 B2 (issued Nov. 25, 2003) (the " '881 patent"), pursuant to *Markman v. Westview Instruments, Inc.*, 52 F.3d 967 (Fed.Cir.1995) (en banc), *aff'd*, 517 U.S. 370, 116 S.Ct. 1384, 134 L.Ed.2d 577 (1996). The construction of the disputed claim language of the patents listed above applies to two cases that have been consolidated for all pretrial issues. [FN1] (*See* Docket Item ["D.I."] 87, 91, C.A. No. 02-1512-KAJ; D.I. 31, C.A. No. 03-120-KAJ.) The plaintiffs in both cases are Abbott Laboratories, Fournier Industrie et Santé, and Laboratoires Fournier S.A. [FN2] (collectively, "Abbott"). The defendants in C.A. No. 02-1512-KAJ are Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Limited (collectively, "Teva"). The defendant in C.A. No. 03-120-KAJ is Impax Laboratories, Inc. ("Impax"). The parties have fully briefed and argued their positions. Jurisdiction is proper under 28 U.S.C. § 1338.

FN1. Because this opinion addresses two cases, each containing its own pleadings, citations will be designated by case number as well as docket item number.

FN2. Fournier Industrie et Santé and Laboratoires Fournier S.A. are collectively referred to as "Fournier."

II. BACKGROUND

A. Procedural Background

Abbott filed a complaint for patent infringement under 35 U.S.C. § 271(e)(2) [FN3] against Teva on October 4, 2002, after Teva submitted an abbreviated new drug application ("ANDA") under 21 U.S.C. § 355(j) prior to the expiration of the patents-in-suit. (D.I.1, C.A. No. 02-1512-KAJ). Teva's ANDA sought approval to sell fenofibrate tablets in 54mg and 160mg dosages. (*Id.*) Teva filed an answer on November 15, 2002 and asserted patent counterclaims for injunctive relief and declaratory judgment of non-infringement of the patents-in-suit, invalidity of the patents-in-suit, and unenforceability of "at least the '726 patent" (D.I. 20 at ¶ 72, C.A. No. 02-1512-KAJ), and antitrust counterclaims for "declaratory judgment and injunctive relief based on [Abbott's] threatened unlawful exclusion of Teva from competition in the manufacture, marketing, and sale of TRICOR® tablets, a cholesterol-lowering drug containing the active pharmaceutical ingredient, fenofibrate, and their generic bioequivalents" [FN4] (*id.* at ¶ 73). Abbott filed a reply to Teva's counterclaims, denying that the patents at issue are not infringed, invalid, or unenforceable. (D.I. 39 at at ¶ 72, C.A. No. 02-1512-KAJ.) Abbott and Teva are scheduled to try this case beginning on June 20, 2005. (D.I. 91 at 7, C.A. No. 02-1512-KAJ.)

FN3. 35 U.S.C. § 271(e)(2) states in relevant part: "It shall be an act of infringement to submit-(A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act ... for a drug claimed in a patent or the use of which is claimed in a patent...." Section 505(j) of the Federal Food, Drug, and Cosmetic Act corresponds to 21 U.S.C. § 355(j).

FN4. By stipulation, Teva's antitrust counterclaims were dismissed without prejudice on January 31, 2003. (D.I.38.)

Abbott filed a complaint for patent infringement under 35 U.S.C. § 271(e)(2) against Impax on January 23, 2003, after Impax submitted an abbreviated new drug application ("ANDA") under 21 U.S.C. § 355(j) prior to the expiration of the patents-in-suit. (D.I.1, C.A. No. 03-120-KAJ.) Impax's ANDA also sought approval to sell fenofibrate tablets in 54mg and 160mg dosages. (*Id.*; D.I. 172 at 3.) Impax filed an answer on March 10, 2003 and asserted a counterclaim for declaratory judgment that the patents-in-suit are invalid, unenforceable and not infringed. (D.I. 9 at ¶ 13, C.A. No. 03-120-KAJ.) Abbott filed a reply to Impax's counterclaim, denying that the patents at issue are not infringed, invalid, or unenforceable. (D.I. 12 at ¶ 13, C.A. No. 03-120-KAJ.) Abbott and Impax are scheduled to try this case beginning on June 6, 2005. (D.I. 53 at 7, C.A. No. 03-120-KAJ.)

B. The Disclosed Technology

1. The State of the Art

*2 Fenofibrate is a pharmaceutical substance that has long been used for treating certain types of cholesterol problems in adults. (D.I. 237 at 1, C.A. 02-1512-KAJ.) Specifically, it lowers triglyceride (fat-like substances) and LDL cholesterol levels in the blood and increases HDL cholesterol levels. [FN5] (Plaintiff's *Markman* Presentation at 2.) Fenofibrate has also "proven effective in reducing a person's risk of heart disease." (*Id.*) To be therapeutically effective, fenofibrate must dissolve in a patient's stomach. (*Id.* at 3.) Dissolved fenofibrate is "converted by the body into fenofibric acid," which can then enter the patient's blood stream. (Plaintiff's *Markman* Presentation at 3.) The major drawback in its usefulness in treating patients is that it has poor hydrosolubility, meaning it does not dissolve easily in water, which makes up the majority of digestive juices in the stomach. (D.I. 237 at 1, C.A. 02-1512-KAJ; Plaintiff's *Markman* Presentation at 4.) Because of this drawback, "only a small percentage of fenofibrate in [prior art] fenofibrate compositions would be absorbed by the body and find its way into the patient's blood stream." (D.I. 237 at 1-2, C.A. 02-1512-KAJ.)

FN5. LDL cholesterol is commonly referred to as unhealthy or "bad cholesterol," whereas HDL cholesterol is referred to as healthy or "good cholesterol." Plaintiff's *Markman* Presentation at 2.)

2. The Stamm Patents

The four patents-in-suit, the '405, '552, '670, and '881 patents (collectively, "the Stamm patents") are related to each other and all have the same inventors Andre Stamm and Pawan Seth. (D.I. 237 at 2, C.A. 02-1512-KAJ.) The Stamm patents are owned by assignment by Fournier and exclusively licensed in

the United States to Abbott. (D .I. 1 at ¶ ¶ 7-8, C.A. 02-1512-KAJ.) The '405, '552, and '881 patents issued as a series of continuations from the same parent application, which itself issued as the '670 patent. (*Id.*) The Stamm patents claim priority to French patent application FR 97 00479 (filed January 17, 1997), and all have the same specification. (*Id.*; D.I. 223 at 3, C.A. 02-1512-KAJ.) Because of this commonality, they also have many of the same claim terms.

The inventions claimed in the Stamm patents relate to a "novel pharmaceutical composition having high bioavailability through improved dissolution, and a method for preparing it." (*See, e.g.*, '881 patent, Background of the Invention, col. 1 ll. 20-22.) In general, this "novel pharmaceutical composition" is described as "an immediate release fenofibrate composition." ('881 patent, col. 3 ll. 38-39.) More specifically, the '670 and '552 patents are directed to fenofibrate compositions with particular ingredients that are described in the claims (*see, e.g.*, '670 patent, col. 9 ll. 48-60; '552 patent, col. 9 l. 66-col. 10 l. 4), whereas the '405 and '881 patents are generally directed to fenofibrate compositions with particular dissolution characteristics (e.g., dissolution rates at particular time intervals) that are described in the claims (*see, e.g.*, '405 patent, col. 10 ll. 29-36; '881 patent, col. 10 ll. 44-65).

III. APPLICABLE LAW

*3 Patent claims are construed as a matter of law. *Markman*, 52 F.3d at 979. A court's objective is to determine the ordinary and customary meaning, if any, that those of skill in the art would apply to the language used in the patent claims. *Waner v. Ford Motor Co.*, 331 F.3d 851, 854 (Fed.Cir.2003) (citing *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1342 (Fed.Cir.2001)). In this regard, pertinent art dictionaries, treatises, and encyclopedias may assist a court. *Texas Digital Sys., Inc. v. Telegenix, Inc.*, 308 F.3d 1193, 1202-03 (Fed.Cir.2002). The intrinsic record, however, is the best source of the meaning of claim language. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed.Cir.1996). Therefore, patent claims are properly construed only after an examination of the claims, the specification, and, if in evidence, the prosecution history of the patent. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1324 (Fed.Cir.2003) (citing *Vitronics*, 90 F.3d at 1582).

The intrinsic record is also of prime importance when claim language has no ordinary meaning in the pertinent art, *see Bell Atl. Network Servs., Inc. v. Covad Communications Group, Inc.*, 262 F.3d 1258, 1269-70 (Fed.Cir.2001) (determining that claim language could only be construed with reference to the written description) (citation omitted), and where claim language has multiple potentially applicable meanings, *Texas Digital, Inc.*, 308 F.3d at 1203.

If patent claim language has an ordinary and accustomed meaning in the art, there is a heavy presumption that the inventor intended that meaning to apply. *Bell Atl. Network Servs., Inc.*, 262 F.3d at 1268 (citing *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 989 (Fed.Cir.1999)). Thus, unless the inventor has manifested an express intent to depart from that meaning, the ordinary meaning applies. *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1325 (Fed.Cir.2002) (citation omitted).

To overcome that presumption, an accused infringer may demonstrate that "a different meaning is clearly set forth in the specification or ... the accustomed meaning would deprive the claim of clarity." *N. Telecom Ltd. v. Samsung Elecs. Co., Ltd.*, 215 F.3d 1281, 1287 (Fed.Cir.2000). However, the presumption may not be rebutted "simply by pointing to the preferred embodiment...." *Teleflex, Inc.*, 299 F.3d at 1327. It may be rebutted, though, where "the patentee ... deviate[d] from the ordinary and accustomed meaning ... by redefining the term or by characterizing the invention in the intrinsic record using words or expressions of manifest exclusion or restriction, representing a clear disavowal of claim scope." *Id.*

If claim language remains unclear after review of the intrinsic record, a court "may look to extrinsic evidence to help resolve the lack of clarity." *Interactive Gift Express, Inc. v. Compuserve Inc.*, 256 F.3d 1323, 1332 (Fed.Cir.2001). The use of extrinsic evidence in the claim construction process, however, is "proper only when the claim language remains genuinely ambiguous after consideration of the intrinsic evidence." *Id.* (citation omitted). A court may not use extrinsic evidence to contradict the import of the intrinsic record, and if the intrinsic record is unambiguous, extrinsic evidence is entitled to no weight. *Bell & Howell Document Mgmt. Prods. Co. v. Altek Sys.*, 132 F.3d 701, 706 (Fed.Cir.1997).

IV. CLAIM CONSTRUCTION

*4 Abbott alleges that Teva infringes claims of each of the Stamm patents, including: claims 1-3, 5, 7, 9, 15,

19, and 35 of the '670 patent; claims 1-12, 15-22, 25, 27, and 56-57 of the '552 patent; claims 6 and 9 of the '405 patent; and claims 5, 10, 19, 26, 31, and 41 of the '881 patent. (D.I. 223 at 4, C.A. 02-1512-KAJ.) Abbott further alleges that Impax infringes claims of three [FN6] of the Stamm patents, including: claims 1-8, 11, 25, 27, and 56 of the '552 patent; claims 6 and 9 of the '405 patent; and claims 5, 10, 14, 19, 26, 31, and 41 of the '881 patent. (D.I. 169 at 1, C.A. 03-120-KAJ.) Because the parties have agreed that the disputed claim terms have the same meaning in each of the asserted claims of the Stamm patents, I will construe each term only once and will provide as a reference, a claim which represents how such term is used in the patents. (D.I. 297 at 32:25-33:10, transcript of *Markman* hearing, Feb. 28, 2005.)

FN6. Initially, Abbott alleged that Impax infringed claims of the '670 patent, but Abbott has since agreed not to assert the '670 patent against Impax in this litigation. (D.I. 297 at 28:11-14, transcript of *Markman* hearing, Feb. 28, 2005.)

A. "inert hydrosoluble carrier"

Claim 1 of the '670 patent, which is representative of the use of this term in the Stamm patents, is as follows:
An immediate-release fenofibrate composition comprising:
(a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form having a size less than 20 m, a hydrophilic polymer and a surfactant; and
(b) optionally one or several outer phase(s) or layer(s), wherein, based on the weight of (a), said inert hydrosoluble carrier makes up from 20 to 50% by weight, said fenofibrate makes up from 20 to 45% by weight, said hydrophilic polymer makes up from 20 to 45% by weight, and said surfactant makes up from 0.1 to 3% by weight.

('670 patent, col. 9 ll. 48-60 (emphasis added).)

1. The Parties' Proposed Constructions

Abbott argues that the specification explicitly defines this claim term as follows: "In the framework of this invention, the expression 'inert hydrosoluble carrier' means any excipient, generally hydrophilic, pharmaceutically inert, crystalline or amorphous, in a particulate form, not leading to a chemical reaction under the operating conditions employed, and which is soluble in an aqueous medium, notably in a gastric acid medium." (D.I. 237 at 6, C.A. 02-1512-KAJ; '670 patent, col. 4 ll. 3-9.) Based on that language, Abbott asserts that "the patentees acted as their own lexicographer [s] by expressly defining the term in the patent specification and by using their definition in a consistent way throughout the patent." (D.I. 237 at 6, C.A. 02-1512-KAJ.) Abbott therefore proposes that I construe "inert hydrosoluble carrier" in accordance with the definition stated in the specification (D.I. 238 at 1, C.A. 02-1512-KAJ; D.I. 167 at 1, C.A. 03-120-KAJ), because "under well-settled law, this express definition 'controls' the meaning of the claim term" (D.I. 237 at 6, C.A. 02-1512-KAJ).

Teva proposes that I construe "an inert hydrosoluble carrier" to mean "any excipient, generally hydrophilic, pharmaceutically inert, crystalline or amorphous, in a particulate form, not leading to a chemical reaction under the operating conditions employed, which is soluble in an aqueous medium, notable in a gastric acid medium, and which functions as a support for particles of micronized fenofibrate and polymer." (D.I. 238 at 1-2, C.A. 02-1512-KAJ.) Teva asserts that the addition of the phrase "and which functions as a support for particles of micronized fenofibrate and polymer" is necessary because "[t]he inert hydrosoluble carrier is a specific material that carries or supports particles of micronized fenofibrate that adhere to the surface of the carrier," and, as such, the meaning of the term should include this functional description in addition to the definition provided in the specification of the Stamm patents. (D.I. 223 at 29-30, C.A. 02-1512-KAJ.) In support, Teva cites several Federal Circuit decisions in which the Court construed disputed claim language to include functional characteristics. [FN7]

FN7. In support of its argument, Teva cites *Astrazeneca AB, Aktiebolaget Hassle, KBI-E, Inc. v. Mutual Pharm. Co., Inc.*, 384 F.3d 1333, 1338-39 (Fed.Cir.2004), *Alloc, Inc. v. Int'l Trade Comm'n*, 342 F.3d 1361, 1371-72 (Fed.Cir.2003), *Networld LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed.Cir.2001), and *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1216-17 (Fed.Cir.1995). (D.I. 268 at 12, C.A. 02-1512-KAJ.)

***5** Impax proposes that I construe "an inert hydrosoluble carrier" in essentially the same way, with this slightly different wording: "an excipient, generally hydrophilic, pharmaceutically inert, crystalline or amorphous, in a particulate form, not

leading to a chemical reaction under the operating conditions employed, which is soluble in an aqueous medium, notably in a gastric acid medium, and having material coated or layered onto the excipient, which acts as a support." (D.I. 167 at 1, C.A. 03-120-KAJ.) Impax asserts that Abbott's proposed construction "fails to account for the meaning of the term 'carrier,' ... [which] must be construed to require that the excipient ... have material coated or layered onto it ... [because] it is acting as the support for the material." (D.I. 169 at 11, C.A. 03-120-KAJ.)

2. The Court's Construction

"[P]atent law permits the patentee to choose to be his or her own lexicographer by clearly setting forth an explicit definition for a claim term that could differ in scope from that which would be afforded by its ordinary meaning." *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1342 (Fed.Cir.2001). A patentee acts as his own lexicographer where he "clearly set [s] forth a definition of the disputed claim term in the specification." *Sunrace Roots Enter. Co. v. SRAM Corp.*, 336 F.3d 1298, 1304 (Fed.Cir.2003). In so doing, "the specification must have sufficient clarity to put one reasonably skilled in the art on notice that the inventor intended to redefine the claim term." *Merck & Co., Inc. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1370 (Fed.Cir.2005) (internal citations omitted).

The patentees here acted as their own lexicographers in defining the meaning of the term "inert hydrosoluble carrier." The specification clearly states, "[i]n the context of this invention, the expression 'inert hydrosoluble carrier' means ...." [FN8] ('670 patent, col. 4 ll. 3-5.) I cannot imagine a clearer way of expressing the intention that a particular term be given a particular meaning. Abbott proposes that such meaning defines the term in its entirety, whereas Teva and Impax argue that the meaning is incomplete because it does not describe the function of the carrier as a support. (D.I. 237 at 6, C.A. 02-1512-KAJ; D.I. 223 at 29-30, C.A. 02-1512-KAJ; D.I. 169 at 11, C.A. 03-120-KAJ.) In acting as their own lexicographers, the patentees identified "inert hydrosoluble *carrier*" as the term they intended to define. ('670 patent, col. 4. ll 3-4 (emphasis added).) Thus, the definition explicitly identified in the specification, was intended to include the term "carrier," and, as such, it does not require its own independent construction based on its intended function. [FN9] Therefore, I construe "inert hydrosoluble carrier" to mean "any excipient, generally hydrophilic, pharmaceutically inert, crystalline or amorphous, in a particulate form, not leading to a chemical reaction under the operating conditions employed, and which is soluble in an aqueous medium, notably in a gastric acid medium."

FN8. Because each of the Stamm patents has the same written description, citations are directed to the patent specification containing the specific claim chosen to represent the context of the disputed claim term at issue.

FN9. In support of its argument, Teva cites *Astrazeneca AB, Aktiebolaget Hassle, KBI-E, Inc. v. Mutual Pharm. Co., Inc.*, where the Federal Circuit held that the patentee had acted as his own lexicographer because the specification stated that "[t]he solubilizers suitable according to the invention are defined below" and then stated that "[t]he solubilizers suitable for the preparations according to the invention are semi-solid or liquid non-ionic surface active agents...." *Astrazeneca*, 384 F.3d 1333, 1339 (Fed.Cir.2004). Based on this disclosure in the specification, the Court determined that the term "solubilizer" was intentionally limited to "surfactants." *Id.* at 1339-40. Thus, if anything, this case supports Abbott's argument that the patentees acted as their own lexicographers in defining the term "inert hydrosoluble carrier," as expressed in the specification. In *Alloc, Inc. v. International Trade Commission*, 342 F.3d 1361, 1371-72 (Fed.Cir.2003), *Networld LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed.Cir.2001), and *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1216-17 (Fed.Cir.1995), also cited by Teva, the patentee had not acted as his own lexicographer by explicitly defining a claim term. Those cases therefore do not support the particular arguments asserted by Teva and Impax, that the explicit definition provided by the patentee is somehow deficient because it does not encompass the full meaning of the term as used in the patents, and, therefore, the court should alter the definition provided.

B. "hydrosoluble carrier"

***6** Claim 1 of the '405 patent, which is representative of the use of this term in the Stamm patents, is as follows:

A composition comprising a hydrosoluble carrier and micronized fenofibrate having a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or with 0.025M sodium lauryl sulfate.

('405 patent, col. 10 ll. 29-36 (emphasis added).)

1. The Parties' Proposed Constructions

The parties propose the same meanings for the term "hydrosoluble carrier" as they did for "inert hydrosoluble carrier," except without it being "pharmaceutically inert." (*See* D.I. 238 at 4, C.A. 02-1512-KAJ; D.I. 167 at 3, C.A. 03-120-KAJ.) Thus, Abbott proposes that I construe "hydrosoluble carrier" to mean "any excipient, generally hydrophilic, crystalline or amorphous, in a particulate form, and which is soluble in an aqueous medium, notably in a gastric acid medium." (D.I. 238 at 4, C.A. 02-1512-KAJ.) Teva and Impax have not specifically set out their proposed meanings for this term, but I understand that their proposals would contain the same functional descriptions following the meaning proposed by Abbott. (*See* D.I. 238 at 4, C.A. 02-1512-KAJ; D.I. 167 at 3, C.A. 03-120-KAJ.)

2. The Court's Construction

Based on my construction of "inert hydrosoluble carrier," *supra* Part IV.A.2., and for the same reasons expressed therein, I construe "hydrosoluble carrier" to mean "any excipient, generally hydrophilic, crystalline or amorphous, in a particulate form, and which is soluble in an aqueous medium, notably in a gastric acid medium."

C. "hydrophilic polymer"

Claim 1 of the '670 patent, which is representative of the use of this term in the Stamm patents, is as follows:
An immediate-release fenofibrate composition comprising:
(a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form having a size less than 20 m, a hydrophilic polymer and a surfactant; and
(b) optionally one or several outer phase(s) or layer(s), wherein, based on the weight of (a), said inert hydrosoluble carrier makes up from 20 to 50% by weight, said fenofibrate makes up from 20 to 45% by weight, said hydrophilic polymer makes up from 20 to 45% by weight, and said surfactant makes up from 0.1 to 3% by weight.

('670 patent, col. 9 ll. 48-60 (emphasis added).)

1. The Parties' Proposed Constructions

Abbott proposes that I construe the term "hydrophilic polymer" to mean "any high molecular weight compound of repeating molecular units having an affinity towards water." (D.I. 238 at 5, C.A. 02-1512-KAJ; D.I. 167 at 4, C.A. 03-120-KAJ.) Abbott asserts that its proposed construction is consistent with the ordinary and customary meaning of the term. (D.I. 237 at 8, C.A. 02-1512-KAJ.) Teva and Impax each propose that I construe "hydrophilic polymer" to mean "any high molecular weight substance (greater, for example, than 300) having sufficient affinity towards water to dissolve therein and form a gel." (D.I. 238 at 5, C.A. 02-1512-KAJ; D.I. 167 at 4, C.A. 03-120-KAJ.) Teva and Impax allege that the patentees acted as their own lexicographers because the specification clearly defines this term when it states, "[t]he expression 'hydrophilic polymer' in the invention should be taken to mean any high molecular weight substance (greater, for example, than 300) having sufficient affinity towards water to dissolve therein and form a gel." ('670 patent, col. 4 ll. 14-17; *see* D.I. 238 at 5, C.A. 02-1512-KAJ; D .I. 268 at 11, C.A. 02-1512-KAJ; D.I. 167 at 4, C.A. 03-120-KAJ.)

*7 Abbott asserts that the construction proposed by Teva and Impax rests on a selective reading of the specification and is at odds with a passage in the specification which states "[d]epending on polymer solubility, [the hydrophilic polymer] *either* dissolves in the solution *or* forms a gel *or* a suspension having varying degrees of thickness." (D.I. 270 at 13, C.A. 02-1512-KAJ; '670 patent, col. 6 ll. 25-27 (emphasis added).) Abbott argues that the definition provided in the specification is inconsistent with the usage of the term in the passage just quoted, because the definition requires that the hydrophilic polymer both dissolve in water *and* form a gel. (D.I. 270 at 12-13, C.A. 02-1512-KAJ.) Because of this alleged inconsistency, Abbott argues that the term should be construed according to its ordinary meaning. (*Id.*)

Teva and Impax assert that Abbott's alleged inconsistency is not an actual inconsistency at all.

They argue that the sentence quoted by Abbott is consistent with the specification's definition of "hydrophilic polymer" because it states that the hydrophilic polymer can either dissolve or form a gel or a suspension "in the solution," which is a suspension of the active ingredient in a solvent, where the solvent can be aqueous or organic. (D.I. 268 at 10-11, C.A. 02-1512-KAJ; D.I. 205 at 10, C.A. 03-120-KAJ.) Thus, Teva and Impax argue that because PVP, the identified hydrophilic polymer, is known to be soluble in water, but insoluble in many organic solvents, such as hydrocarbons or mineral oil, the term "hydrophilic polymer" is used consistently throughout the specification. (*Id.*) Therefore, they assert that "hydrophilic polymer" should be construed as explicitly defined in the specification and Abbott's proposed construction should be rejected. (*Id.*)

2. The Court's Construction

For the same reasons expressed *supra* Part IV.A.2., I find that the patentees acted as their own lexicographers and specifically defined "hydrophilic polymer" in the specification to mean "any high molecular weight substance (greater, for example, than 300) having sufficient affinity towards water to dissolve therein and form a gel." Furthermore, because I find that the specification uses this term consistently, I agree with Teva and Impax that the presumption, stating that a term should be construed according to its ordinary meaning, is overcome.

First, the specification clearly and explicitly defines the term "hydrophilic polymer," when it states "[t]he expression 'hydrophilic polymer' in the invention should be taken to mean ...." ('670 patent, col. 4 ll. 14-15.) Second, the portion of the specification identified by Abbott, discussing polymer solubility, does not establish an inconsistency with regard to how the patentees used this term in the patent. This paragraph states in its entirety:

The significant starting product is the suspension of the active ingredient. This suspension is prepared by putting the micronized active ingredient into suspension in a solution comprising the hydrophilic polymer and, optionally, a surfactant, in solution in a solvent. If a surfactant is employed, it is put into solution in the solvent (beaker+magnetic or vane stirrer). Next, the hydrophilic polymer (PVP) is dispersed, while stirring, in the solution previously obtained. *Depending on polymer solubility, this either dissolves in the solution or forms a gel or a suspension* having varying degrees of thickness. While still stirring, the micronized active ingredient is dispersed in the form of a fine shower into the above solution or suspension, to form a homogenous suspension. The order of these steps can be reversed. *The solvent employed can be aqueous or organic* (for example ethanol). For example demineralized water can be used.

***8** ('670 patent, col. 6, ll. 16-32 (emphasis added).)

As noted by Abbott, this portion of the specification states that the hydrophilic polymer "either dissolves in the solution or forms a gel or a suspension," but does not both dissolve and form a gel, as the portion of the specification defining the term requires. Counsel for Abbott, however, was unable to articulate for the court why the statement "[t]he solvent employed can be aqueous or organic" does not relieve any perceived inconsistency in the use of the term hydrophilic polymer. (*See* D.I. 297 at 60:24-72:3, transcript of *Markman* hearing, Feb. 28, 2005.)

It is quite clear that when the polymer either dissolves or forms a gel or suspension, it is doing so in "the solution." "The solution" thus referred to is the suspension, which consists of the micronized active ingredient, the hydrophilic polymer, optionally a surfactant, and a solvent. Thus, the suspension contains a solvent. Further, the penultimate sentence in the paragraph makes clear that the solvent can be aqueous or organic. As noted by Teva, PVP, the hydrophilic polymer discussed in the quoted paragraph, "is known to be soluble in water but insoluble in many organic solvents." (D.I. 268 at 10, C.A. 02-1512-KAJ.) Thus, I agree with Teva and Impax, that if the suspension contained an aqueous solvent, the polymer would be affected differently than if the suspension contained an organic solvent. Such a difference would explain why this portion of the specification states that the hydrophilic polymer "either dissolves in the solution *or* forms a gel *or* a suspension," rather than stating that the hydrophilic polymer dissolves *and* forms a gel, as its definition requires it to do in water. Thus, the specification does not use the term "hydrophilic polymer" in a manner inconsistent with the explicit definition provided by the patentees acting as their own lexicographers, and, therefore, I construe it to mean "any high molecular weight substance (greater, for example, than 300) having sufficient affinity towards water to dissolve therein and form a gel."

D. "granuate"

Claim 1 of the '552 patent, which is representative of

the use of this term in the Stamm patents, is as follows: A fenofribrate composition comprising granulates, wherein the granulates comprise micronized fenofibrate having a particle size below 20 m, inert hydrosoluble carrier particles and at least 20% by weight of at least one hydrophilic polymer, wherein the weight ratio of fenofibrate to hydrophilic polymer is from 1/10 to 4/1.

('552 patent, col. 9 l. 66-col. 10 l. 4 (emphasis added).)

1. The Parties' Proposed Constructions

Abbott proposes that I construe the term "granulate" to mean "a small grain or pellet, or small particles forming a larger unit." (D.I. 238 at 6, C.A. 02-1512-KAJ; D.I. 167 at 5, C.A. 03-120-KAJ.) Abbott argues that its proposed construction is consistent with the ordinary and customary meaning of "granulate." (D.I. 237 at 11.) Teva proposes that I construe "granulate" to mean "the carrier to which the hydrophilic polymer and fenofibrate are adhered as single particles or as agglomerates, forming a coated-core structure." (D.I. 238 at 6, C.A. 02-1512-KAJ.) Impax proposes that I construe "granulate" to mean "the product generated from a granulation process having structures consisting of an inert hydrosoluble carrier coated with micronized fenofibrate and a hydrophilic polymer or (the remnants of) some solvent for fenofibrate. (D.I. 167 at 5-6, C.A. 03-120-KAJ.) Teva and Impax each assert that based on disclosures in the specification, the "very character of the invention" is the coated-core structure, and, as such, it should be a part of every embodiment. (D.I. 223 at 35-36, C .A. 02-1512-KAJ; D.I. 169 at 12-13, C.A. 03-120-KAJ.)

2. The Court's Construction

***9** As earlier noted, if patent claim language has an ordinary and accustomed meaning, there is a heavy presumption that the inventor intended that meaning to apply. *Bell Atlantic*, 262 F.3d at 1268. The ordinary meaning of "granulate," as a verb, is "to form ... into ... granules." Webster's Third New International Dictionary 989 (3d ed.1986). In the context of the Stamm patents, however, the patentee clearly intends to use the term "granulate" as a noun, synonymous with "granule," whose ordinary and plain meaning is "one of a number of particles forming a larger unit." *Id.*

Neither Teva nor Impax has presented sufficient evidence to demonstrate that the patentee intended another meaning to apply. First, as noted in the foregoing discussion, *see supra* Parts IV.A. and IV.C., when the patentees intended to give a word or phrase a particular meaning, rather than simply relying on an ordinary and customary meaning, they did so in unmistakable terms. Second, Impax's proposed construction includes structural features of the preferred embodiment formed by the preferred process described in the specification. Specifically, Impax cites two statements in the specification regarding "[t]he composition according to the invention," which refer to methods of preparing the composition. (*See* D.I. 169 at 13, C.A. 03-120-KAJ (citing D.I. 170, Ex. 4 at 6:3-7; 6:43-47).) Each of these statements, however, is part of the detailed description of the preferred embodiment. Further, product claims are generally not limited to the process by which the product is made. *See Vanguard Prods. Corp. v. Parker Hannifin Corp.*, 234 F.3d 1370, 1372 (Fed.Cir.2000) (noting that product claims are not generally limited to the process by which such product is made); *3M Innovative Props. Co. v. Avery Dennison Corp.*, 350 F.3d 1365, 1374 (Fed.Cir.2003) (construing the term "embossed" as referring to an embossed pattern without "limit[ing] how the embossed pattern, as defined in the specification, is created") (emphasis omitted). Third, "granulate" is a "general descriptive term," defined subsequently in the claim which does not impose the limitations Teva and Impax seek to impart. Therefore, I construe the term "granulate," synonymously with granule, to mean "one of a number of particles forming a larger unit."

E. "composition"

Claim 1 of the '670 patent, which is representative of the use of this term in the Stamm patents, [FN10] is as follows:

> FN10. I note, however, what appears to be an inconsistency in the prosecution history of the '405 and '881 patents. Claim 1 of the '405 patent, as originally submitted to the patent and trademark office, and claim 1 of the '881 patent, as issued, are identical. (D .I. 170, Ex. 7 at 055, C.A. 03-120-KAJ, Response and Amendment, date stamped Jan. 26, 2001; '881 patent, col. 10, II. 44-65.) In the prosecution history of the '405 patent, the examiner required, and the applicants acquiesced in, adding the term "hydrosoluble

> carrier" to the claim in order to clearly define the composition. (D.I. 235, Ex. 7 at 118, C.A. 02-1512-KAJ, Interview Summary dated Mar. 21, 2001 (stating that "to clearly define the composition ... [it] must comprise the micronized fenofibrate and a hydrosoluble carrier to give the claimed dissolution profile [and that w]ithout the hydrosoluble carrier (i.e. drug alone), the dissolution profile would be different.") However, in prosecuting the '881 patent, a second examiner allowed claim 1 without requiring the addition of the "hydrosoluble carrier" term. ('881 patent, col. 10, II. 44-65.) This would suggest that the term "composition," as used in claim 1 of the '405 patent, was understood by at least one examiner to include a hydrosoluble carrier. Thus, there seems to be an inconsistency in the decisions rendered by the two examiners, because claim 1 of the '405 patent and claim 1 of the '881 patent each claim the same dissolution profile, yet the applicants were not required to amend claim 1 of the '881 patent to include the hydrosoluble carrier as well.

An immediate-release fenofibrate composition comprising:
(a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form having a size less than 20 m, a hydrophilic polymer and a surfactant; and
(b) optionally one or several outer phase(s) or layer(s), wherein, based on the weight of (a), said inert hydrosoluble carrier makes up from 20 to 50% by weight, said fenofibrate makes up from 20 to 45% by weight, said hydrophilic polymer makes up from 20 to 45% by weight, and said surfactant makes up from 0.1 to 3% by weight.

***10** ('670 patent, col. 9 II. 48-60 (emphasis added).)

1. The Parties' Proposed Constructions

Abbott proposes that I construe the term "composition" to mean "a combination of various elements or ingredients." (D.I. 238 at 8, C.A. 02-1512-KAJ; D.I. 167 at 6, C.A. 03-120-KAJ.) Abbott argues that this meaning comports with "its ordinary meaning to a person of skill in the art." (D.I. 237 at 14, C.A. 02-1512-KAJ.) Teva proposes that I construe "composition" to mean "a fenofibrate composition, wherein the inert carrier (as described above) is a support for the micronized fenofibrate (as described below) and hydrophilic polymer (as described above), and which can take the form of granulates, tablets and capsules." (D.I. 238 at 8, C.A. 02-1512-KAJ.) Teva makes the same argument in support of its proposed construction for "composition" that it made for its proposed construction of "granulates," *see supra* Part IV.D.1., namely, that it must be construed to cover the coated-core structure. (D.I. 223 at 34-36.) Impax proposes that I construe "composition" to mean "a structure wherein an inert hydrosoluble carrier is coated with micronized fenofibrate and a hydrophilic polymer or (the remnants of) some solvent for fenofibrate." (D.I. 167 at 6, C.A. 03-120-KAJ.) Impax makes the same argument in support of its proposed construction for "composition" as it made for its proposed construction of "granulates," *see supra* Part IV.D.1., namely, that it must be construed to include the structural limitation of a coating. (D.I. 169 at 12-13, C.A. 03-120-KAJ; D.I. 205 at 11-14; C.A. 03-120-KAJ.)

2. The Court's Construction

For the same reasons expressed in construing the term "granulate," *see supra* Part IV.D.2., I find that the term "composition" should be construed according to its ordinary meaning and thus means "an aggregate, mixture, mass, or body formed by combining two or more elements or ingredients." Webster's Third New International Dictionary 466 (3d ed.1986). As seen in claim 1 of the '670 patent, the elements which combine to form the "composition" are specifically identified. Thus, I agree with Abbott that "composition," is used "as a general descriptive term" (D.I. 270 at 6, C.A. 02-1512-KAJ) and thus I give it the ordinary meaning of "an aggregate, mixture, mass, or body formed by combining two or more elements or ingredients."

F. "tablet"

Claim 15 of the '670 patent, which is representative of the use of this term in the Stamm patents, is as follows:
The composition according to claim 1, under the form of a tablet.

('670 patent, col. 10, II. 46-47 (emphasis added).)

1. The Parties' Proposed Constructions

Abbott proposes that I construe the term "tablet" to mean "an oral dosage form consisting of a small mass

of medication." (D.I. 238 at 7, C.A. 02-1512-KAJ; D.I. 167 at 8, C.A. 03-120-KAJ.) Teva proposes that I construe "tablet" to mean something "made from the compression of granulates (as described below) together with an outer phase." (D.I. 238 at 7, C.A. 02-1512-KAJ.) Teva agrees that the meaning of the term encompasses an "oral dosage form." (D.I. 268 at 15, C.A. 02-1512-KAJ ("Solely insofar as this is concerned, Teva does not oppose this construction....").) Impax proposes that I construe "tablet" to mean "an oral dosage form made from compressed structures wherein an inert hydrosoluble carrier is coated with micronized fenofibrate and a hydrophilic polymer or (the remnants of) some solvent for fenofibrate." (D.I. 167 at 8-9, C.A. 03-120-KAJ.)

***11** Abbott argues that the term "tablet" should be construed according to its ordinary meaning to a person of skill in the art, and that the term is used in a manner consistent with its ordinary meaning. (D.I. 270 at 7, C.A. 02-1512-KAJ.) Teva and Impax make essentially the same arguments they made with regard to "composition" and "granulate," namely that the tablets are a type of "composition" which requires the coated-core structure. (*See* D.I. 268 at 15, C.A. 02-1512-KAJ; D.I. 205 at 15-16, C.A. 03-120-KAJ.) Additionally, Teva and Impax propose that the term should be construed to include the method by which it is made (i.e.compression) and the elements which comprise it (i.e., granulates with an outer phase, as proposed by Teva, or an inert hydrosoluble coated carrier, etc., as proposed by Impax). (*See* D.I. 238 at 7, C.A. 02-1512-KAJ; D.I. 167 at 8-9, C.A. 03-120-KAJ.)

2. The Court's Construction

I agree with Abbott that the term "tablet" should be accorded its ordinary and customary meaning in the art as "an oral dosage form consisting of a small mass of medication." (*See* Webster's Third New International Dictionary 2325 (3d ed.1986) (defining "tablet" as "a small mass of medicated material").) The term "tablet" itself should not be construed to include a form of "compression" because subsequent claims in the '670 patent include this limitation. For example, claim 19 of the '670 patent is as follows:
The composition according to claim 15 under the form of a tablet resulting from the compression of elements (a) together with an outer phase.

('670 patent, col. 10, ll. 54-56.) Thus, claim 19 specifically claims a tablet resulting from a compression, and also discloses the specific elements which comprise it. "Elements (a)," refers to the elements listed in claim 1, which include: "an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form having a size less than 20 m, a hydrophilic polymer and a surfactant." ('670 patent, col. 9, ll. 50-53.) Thus, it would be improper to read such limitations into claim 15, when claim 19 expressly contains those precise limitations.

Additionally, Teva cites a portion of the specification which states, "[t]his tablet *preferably* results from the compression of elements (a) (under the form of granules) together with an outer phase." ('670 patent, col. 5, ll. 23-25 (emphasis added).) As indicated by emphasis, this disclosure is of a *preferred* method of making the tablet, not necessarily the only way. Thus, it would be inappropriate to limit the claim term "tablet" to a preferred embodiment. Therefore, in accordance with its customary meaning, I construe the term "tablet" to mean "an oral dosage form consisting of a small mass of medication."

G. "covered"

Claim 1 of the '670 patent, which is representative of the use of this term in the Stamm patents, is as follows:
***12** An immediate-release fenofibrate composition comprising:
(a) an inert hydrosoluble carrier covered with at least one layer containing fenofibrate in a micronized form having a size less than 20 m, a hydrophilic polymer and a surfactant; and
(b) optionally one or several outer phase(s) or layer(s), wherein, based on the weight of (a), said inert hydrosoluble carrier makes up from 20 to 50% by weight, said fenofibrate makes up from 20 to 45% by weight, said hydrophilic polymer makes up from 20 to 45% by weight, and said surfactant makes up from 0.1 to 3% by weight.

('670 patent, col. 9 ll. 48-60 (emphasis added).)

1. The Parties' Proposed Constructions

Abbott proposes that I construe the term "covered" to mean "appearing on or occupying some portion of the surface of." (D.I. 238 at 10.) [FN11] Teva proposes that I construe "covered" to mean "to lie over; spread over; be placed on or often over the whole surface of; envelop, film, coat." (*Id.*)

FN11. Because this claim term appears only in the context of the asserted claims of the '670 patent, which Abbott is not asserting against Impax, Impax has not offered a proposed construction for this term and therefore all citations in Part IV.G. are to C.A. 02-1512-KAJ.

2. The Court's Construction

This is a situation where both parties assert that they have proposed the ordinary meaning of the term as understood by a person of skill in the art. (*See* D.I. 237 at 16; D.I. 268 at 15-16.) Each party's proposal finds its origin in a dictionary. In fact, the same dictionary, Webster's Third New International Dictionary 524 (3d ed.1986), contains both definitions proposed by the parties. Although both proposed constructions may seem equally applicable if viewing the claim term in isolation, it is clear when reading the claim term in the context of the claim itself that the patentees intended to impart the construction as proposed by Teva. The claim language states, "covered with at least one *layer.*" ('670 patent, col. 9, II. 50-51 (emphasis added).) The addition of the word "layer" makes it clear that the patentees did not intend for the hydrosoluble carrier to be covered "here and there" with micronized fenofibrate, but rather they intended it to be "enveloped" with micronized fenofibrate, to the extent that the micronized fenofibrate is discernable as a "layer." A covering "here and there" would not be discernable as a "layer," as that term is used in the '670 patent. Additionally, in the Summary of the Invention section, the specification describes that the granules can be coated "with one or several ... layer(s)." ('670 patent, col. 3, ll. 39-40.) Although in a slightly different context, this disclosure indicates that the patentees intended that the composition could have several layers on the inert hydrosoluble carrier core. If "covered" were construed to mean that the inert hydrosoluble carrier were coated "here and there," it is difficult to see how that could be described as multiple "layers," in the context of the disclosures in the specification and the claim language. Thus, I find that, in the context of being "covered with at least one layer," the ordinary and customary meaning of the term "covered" is "enveloped," as in "to be placed on or over the whole surface of."

H. "dissolution medium constituted by water with 2% by weight polysorbate 80 or 0.025 M sodium lauryl sulfate"

***13** Claim 1 of the '881 patent, which is representative of the use of this term in the Stamm patents, is as follows:

A composition comprising micronized fenofibrate, wherein the composition has a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or 0.025 M sodium lauryl sulfate.

('881 patent, col. 10 II. 44-65 (emphasis added).)

1. The Parties' Proposed Constructions

Abbott proposes that I construe the term "dissolution medium constituted by water with 2% by weight polysorbate 80 or 0.025 M [i.e. molar] sodium lauryl sulfate" to mean "one of two solutions in water: one with a concentration of 2% by weight polysorbate 80 and one with a concentration of 0.025 molar sodium lauryl sulfate." (D.I. 270 at 13.) Teva proposes that I find that this phrase "is indefinite and incapable of construction." (D.I. 223 at 38.) [FN12]

FN12. Although this term appears in several claims asserted against Impax, Impax has not disputed Abbott's proposed construction of this term in their briefs on claim construction, and as such, all citations in Part IV.H. are to C.A. 02-1512-KAJ. (*See* D.I. 169, 205.)

Teva asserts that this claim term is indefinite because it means that "an unknown amount of 0.025M sodium lauryl sulfate solution is added to an unknown amount of water." (D.I. 223 at 37.) In support, Teva cites to two disclosures in the specification, one where the dissolution medium is defined as consisting "of 1000 ml of water to which 0.025M sodium lauryl sulfate sodium is added ..." ('881 patent, col. 2 ll. 28-30) and one which describes "a dissolution medium constituted by water with 0.025M sodium lauryl sulfate" ('881 patent, col. 3 II. 56-57). Teva asserts that in each of these disclosures, an unknown amount of 0.025M sodium lauryl sulfate solution is combined with, in the first instance 1000 ml of water, and in the second instance, an unknown amount of water. (D.I. 223 at 28.)

In response, Abbott asserts that a person of skill in the art, would understand the claim language and the disclosures in the specification as designating a particular concentration of sodium lauryl sulfate,

specifically 0.025M sodium lauryl sulfate. (D.I. 270 at 14.) Further, Abbott asserts that Teva's own expert, Ms. Gray, interpreted this claim term to require a specific concentration, and that she dissolved a sufficient amount of sodium lauryl sulfate in water to obtain 1 liter of a 0.025 molar solution. (*Id.* at 14-15 .)

Teva counters that "Plaintiff's proposed construction ... is legally untenable because it eliminates the term "with" from the claim element...." (D.I. 268 at 9 (emphasis omitted).) Thus, Teva asserts that the claim term is "fatally ambiguous." (*Id.*)

2. The Court's Construction

Although Teva's "grammatical savvy" is noted, I believe that any ambiguity created by the word "with" was likely an inadvertent error. *See Merck*, 395 F.3d at 1371 n. 8 (finding that the omission of the word "about" was likely an inadvertent error, rather than an intentional product of claim drafting). In the context of the Stamm patents, the claim term is understood by persons of ordinary skill in the art as expressing a concentration, rather than a specific volume. (*See* D.I. 267, Ex. K at 4, 5, Expert Report of Vivian Gray (noting that Ms. Gray used 1200 ml of dissolution medium at a concentration of "0.025 M Sodium Lauyrl Sulfate" to test samples provided by Fournier).) Although Ms. Gray also stated that "the wording describing the 0.025 M Sodium Lauryl Sulfate medium was not clear," she was able to test the samples according the methodology disclosed in the Stamm patents. (*Id.* at 5.) Furthermore, Abbott's expert, Dr. Amidon, stated that it is inconceivable that anyone of skill in the art would interpret the claim term in the manner suggested by Teva. [FN13] (*See* D.I. 236, Ex. 11 at 339:4-5, Dep. of Dr. Amidon, Nov. 19, 2004.) Thus, the claim term is not indefinite because one of ordinary skill in the art would read the term as requiring a concentration of 0.025 molar sodium lauryl sulfate. Therefore, I construe "dissolution medium constituted by water with 2% by weight polysorbate 80 or 0.025 M sodium lauryl sulfate" to mean "one of two solutions in water: one with a concentration of 2% by weight polysorbate 80 and one with a concentration of 0.025 molar sodium lauryl sulfate."

FN13. Although at the *Markman* hearing, counsel for Teva argued that Ms. Gray used 0.025 molar sodium lauryl sulfate because the prosecution history discussed testing under those conditions (D.I. 297 at 81:21-82:3, C.A. 02-1512-KAJ), her methodology is persuasive evidence that a person of ordinary skill in the art practicing the invention claimed in the patents would do the same thing, and look to the prosecution history to clarify any perceived ambiguity. Although I do not find that the claim term is ambiguous, I merely note that Ms. Gray and Dr. Amidon's opinions are instructive as to how one of ordinary skill in the art would view the claim term.

V. CONCLUSION

***14** For the reasons stated, the terms in dispute are construed as follows:

CLAIM TERM/PHRASE	THE COURT'S CONSTRUCTION
"inert hydrosoluble carrier"	The Court construed the claim term to mean "any excipient, generally hydrophilic, pharmaceutically inert, crystalline or amorphous, in a particulate form, not leading to a chemical reaction under the operating conditions employed, and which is soluble in an aqueous medium, notably in a gastric acid medium."
"hydrosoluble carrier"	The Court construed the claim term to mean "any excipient, generally hydrophilic, crystalline or amorphous, in a particulate form, and which is soluble in

	an aqueous medium, notably in a gastric acid medium."
"hydrophilic polymer"	The Court construed the claim term to mean "any high molecular weight substance (greater, for example, than 300) having sufficient affinity towards water to dissolve therein and form a gel."
"granulate"	The Court construed the claim term to mean "one of a number of particles forming a larger unit."
"composition"	The Court construed the claim term to mean "an aggregate, mixture, mass, or body formed by combining two or more elements or ingredients."
"tablet"	The Court construed the claim term to mean "an oral dosage form consisting of a small mass of medication."
"covered"	The Court construed the claim term to mean "enveloped," as in "to be placed on or over the whole surface of."
"dissolution medium constituted by water with 2% by weight polysorbate 80 or 0.025 M sodium lauryl sulfate"	The Court construed the claim term to mean "one of two solutions in water: one with a concentration of 2% by weight polysorbate 80 and one with a concentration of 0.025 molar sodium lauryl sulfate."

An appropriate order will issue.

ORDER

For the reasons set forth in the Memorandum Opinion issued today in this matter,

IT IS HEREBY ORDERED that the disputed claim terms in U.S. Patent No. 6,074,670, U.S. Patent No. 6,589,552 B2, U.S. Patent No. 6,277,405 B1, and U.S. Patent No. 6,652,881 B2 are construed as follows:

CLAIM TERM/PHRASE	THE COURT'S CONSTRUCTION
"inert hydrosoluble carrier"	The Court construed the claim term to mean "any excipient, generally hydrophilic, pharmaceutically inert, crystalline or amorphous, in a particulate form, not leading to a chemical reaction under the operating conditions employed, and which is soluble in an aqueous medium, notably in a gastric acid medium."
"hydrosoluble carrier"	The Court construed the claim term to mean "any excipient, generally

	hydrophilic, crystalline or amorphous, in a particulate form, and which is soluble in an aqueous medium, notably in a gastric acid medium."
"hydrophilic polymer"	The Court construed the claim term to mean "any high molecular weight substance (greater, for example, than 300) having sufficient affinity towards water to dissolve therein and form a gel."
"granulate"	The Court construed the claim term to mean "one of a number of particles forming a larger unit."
"composition"	The Court construed the claim term to mean "an aggregate, mixture, mass, or body formed by combining two or more elements or ingredients."
"tablet"	The Court construed the claim term to mean "an oral dosage form consisting of a small mass of medication."
"covered"	The Court construed the claim term to mean "enveloped," as in "to be placed on or over the whole surface of."
"dissolution medium constituted by water with 2% by weight polysorbate 80 or 0.025 M sodium lauryl sulfate"	The Court construed the claim term to mean "one of two solutions in water: one with a concentration of 2% by weight polysorbate 80 and one with a concentration of 0.025 molar sodium lauryl sulfate."

D.Del.,2005.
Abbott Laboratories v. Teva Pharmaceuticals USA, Inc.
Slip Copy, 2005 WL 1026746 (D.Del.)

Briefs and Other Related Documents (Back to top)

- 1:03cv00120 (Docket) (Jan. 23, 2003)
- 1:02cv01512 (Docket) (Oct. 04, 2002)

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HAbbott Laboratories v. Teva Pharmaceuticals USA, Inc., 2005 WL 1026746 (D.Del., Apr 22, 2005) (NO. CIV.A. 02-1512-KAJ, CIV.A. 03-120-KAJ)

History
Direct History

=> 1 **Abbott Laboratories v. Teva Pharmaceuticals USA, Inc.**, 2005 WL 1026746 (D.Del. Apr 22, 2005) (NO. CIV.A. 02-1512-KAJ, CIV.A. 03-120-KAJ)

Subsequent Determination

H 2 Abbott Laboratories v. Teva Pharmaceuticals USA, Inc., 2005 WL 1384769 (D.Del. May 09, 2005) (NO. CIV.A. 02-1512-KAJ)

Related References (U.S.A.)

H 3 Abbott Laboratories v. Teva Pharmaceuticals USA, Inc., 2004 WL 1622427 (D.Del. Jul 15, 2004) (NO. CIV.A. 02-1512-KAJ)

Court Documents
Dockets (U.S.A.)

D.Del.

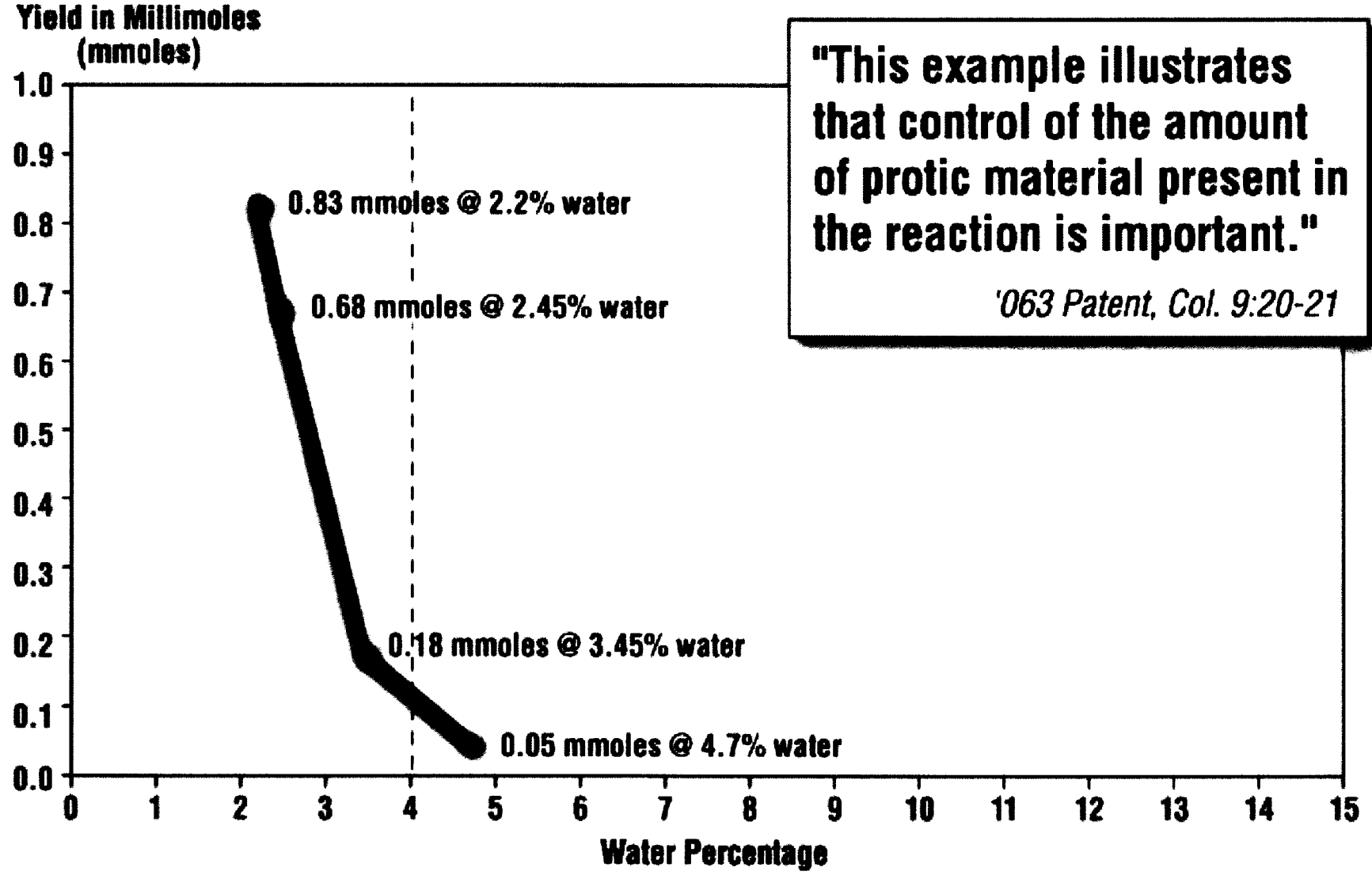
4 ABBOTT LABORATORIES, ET AL v. TEVA PHARMACEUTICALS, NO. 1:02cv01512 (Docket) (D.Del. Oct. 04, 2002)

5 ABBOTT LABORATORIES, ET AL v. IMPAX LABORATORIES, NO. 1:03cv00120 (Docket) (D.Del. Jan. 23, 2003)

Importance of Controlling Protic Material (e.g., Water)

Example 3: When Aniline is a Solvent

RDX-1



"This example illustrates that control of the amount of protic material present in the reaction is important."

'063 Patent, Col. 9:20-21

''063 Patent, Col. 9, Example 3, Table 2

K001

US 20050065376A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2005/0065376 A1**

Wang et al. (43) **Pub. Date: Mar. 24, 2005**

(54) **PROCESS FOR PREPARING 4-AMINODIPHENYLAMINE**

(75) Inventors: **Nongyue Wang**, Cao County (CN); **Ruibiao Yu**, Cao County (CN); **Xiaohui Mao**, Cao County (CN); **Xiaogen Feng**, Cao County (CN); **Qianwen Cheng**, Cao County (CN)

Correspondence Address:
VENABLE, BAETJER, HOWARD AND CIVILETTI, LLP
P.O. BOX 34385
WASHINGTON, DC 20043-9998 (US)

(73) Assignee: **Guangqiang SHI and Nongyue WANG**, Cao County (CN)

(21) Appl. No.: **10/882,677**

(22) Filed: **Jul. 2, 2004**

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Jul. 4, 2003	(CN)	03148565.0
Jul. 4, 2003	(CN)	03148200.7
Jul. 4, 2003	(CN)	03148198.1
Jul. 4, 2003	(CN)	03148196.5

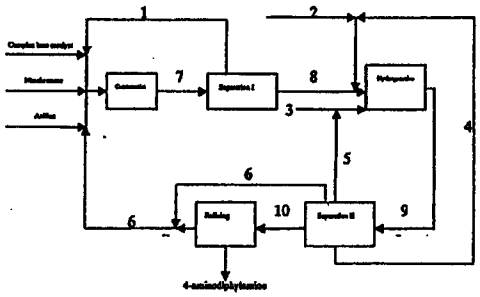
Publication Classification

(51) **Int. Cl.**[7] **C07C 29/36**

(52) **U.S. Cl.** **564/434**

(57) **ABSTRACT**

The present invention discloses a process for preparing 4-aminodiphenylamine, which process uses nitrobenzene and aniline as raw materials, a complex base catalyst as condensation catalyst and a powdery composite catalyst as hydrogenation catalyst, and comprises five process stages: condensation; separation I; hydrogenation; separation II; and refining. The process can be continuously carried out. By selecting a complex base catalyst to catalyze the condensation reaction and separating it prior to the hydrogenation, the problem that the complex base catalysts thermally decompose in the hydrogenation reaction is avoided, the selectable range of hydrogenation catalysts is largely enlarged so that it is possible to select cheaper hydrogenation catalyst, and the selection of production process and equipment is easier and further industrialization is easier. The complex base catalysts used in the present invention are inexpensive and have higher catalytic activity. The process can be carried out at mild conditions and can adapt to broad range of water content, by-product is less and conversion and selectivity are higher. The operational strength is low, no corrosive liquid is produced, and environment pollution is reduced. The purity of 4-aminodiphenylamine prepared can exceed 99 wt.-%, and the yield in the industrial production process can be over 95%.



A flow diagram of the process for preparing 4-aminodiphylamine

1 - reused complex base catalyst

2 - powdery composite catalyst

3 - hydrogenation solvent

4 - reused, optionally at least partially regenerated, powdery composite catalyst

5 - reused hydrogenation solvent

6 - reused aniline

7 - condensation liquid

8 - separation I liquid (i.e., condensation liquid from which the complex base catalyst has been separated)

9 - hydrogenation liquid

10 - crude product of 4-aminodiphylamine

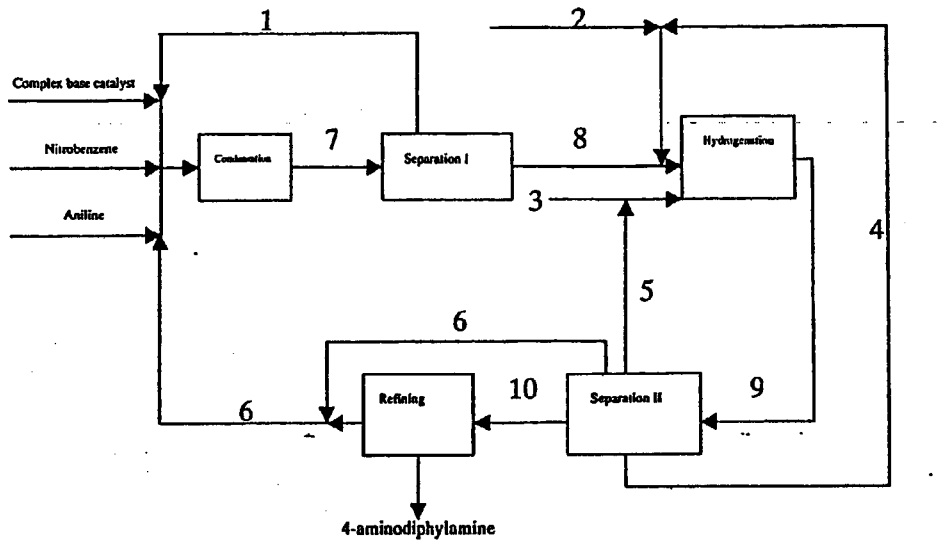


Figure 1. A flow diagram of the process for preparing 4-aminodiphylamine

1 - reused complex base catalyst

2 - powdery composite catalyst

3 - hydrogenation solvent

4 - reused, optionally at least partially regenerated, powdery composite catalyst

5 - reused hydrogenation solvent

6 - reused aniline

7 - condensation liquid

8 - separation I liquid (i.e., condensation liquid from which the complex base catalyst has been separated)

9 - hydrogenation liquid

10 - crude product of 4-aminodiphylamine

PROCESS FOR PREPARING 4-AMINODIPHENYLAMINE

CROSS REFERENCE OF RELATED APPLICATIONS

[0001] The present application claims priority to CN03148566.9, CN03148195.7, CN03148194.9, CN03148191.4, CN03148565.0, CN03148200.7, CN03148198.1, CN03148196.5, filed on Jul. 4, 2003, which are incorporated herein by reference in their entirety and for all purposes.

TECHNICAL FIELD

[0002] The present invention relates to a process for preparing 4-aminodiphenylamine. In particular, the present invention relates to a continuous process for preparing 4-aminodiphenylamine, which process uses nitrobenzene and aniline as raw materials, a complex base catalyst as condensation catalyst and a conventional hydrogenation catalyst or a powdery composite catalyst as hydrogenation catalyst, and comprises five process stages: condensation; separating, recovering and reusing the complex base catalyst; hydrogenation; separating, recovering and reusing aniline and optionally separating, recovering and reusing hydrogenation solvent, and if necessary, separating, recovering and reusing the hydrogenation catalyst which is optionally at least partially regenerated; and refining.

BACKGROUND OF THE INVENTION

[0003] 4-Aminodiphenylamine is an important intermediate of antioxidant and stabilizer, and is an important chemical product for rubber industry and polymer industry. Depending on starting materials, current methods for preparing 4-aminodiphenylamine include: (1) aniline method, wherein p-nitro-chlorobenzene and aniline as raw materials react in the presence of a catalyst to produce 4-nitrodiphenylamine, then 4-nitrodiphenylamine is reduced by sodium sulfide to form 4-aminodiphenylamine; (2) formanilide method, wherein formic acid and aniline are used as starting materials to prepare formanilide, which in turn reacts with p-nitro-chlorobenzene in the presence of an acid-binding agent such as potassium carbonate, to produce 4-nitrodiphenylamine, and then 4-nitrodiphenylamine is reduced by sodium sulfide to form 4-aminodiphenylamine; (3) diphenylamine method, wherein diphenylamine as raw material is nitrosated using a nitrite in an organic solvent to produce N-nitrosodiphenyamine, which rearranges to 4-nitrosodiphenyamine hydrochloride under the action of anhydrous hydrogen chloride, then 4-nitrosodiphenyamine hydrochloride is neutralized with a base to give 4-nitrosodiphenyamine, and said 4-nitrosodiphenyamine is finally reduced to 4-aminodiphenylamine by sodium sulfide. Although these methods use different starting materials, traditional sodium sulfide is used as reducing agent to prepare 4-aminodiphenylamine. These reactions suffers from severe reaction conditions, complex operation, higher energy consumption, lower yield, higher cost and environment pollution caused by concomitant waste water, waste gas and waste residue.

[0004] Among the preparation methods of 4-aminodiphenylamine, one utilizes nitrobenzene or nitrobenzene and aniline or nitrosobenzene as raw materials to carry out condensation reaction, and then utilizes hydrogen gas to perform hydrogenation to produce 4-aminodiphenylamine. In fact, it was reported in 1901 (Wohl, Chemische Berichte, 34, p. 2442 (1901)) and in 1903 (Wohl, Chemische Berichte, 36, p. 4135 (1903)) that nitrobenzene reacted with aniline under the action of a base to form 4-nitrosodiphenylamine and 4-nitrodiphenylamine. However, said method is neither attached importance to nor developed because of its relatively low yield until 1990s when it is researched and developed again and achieved some progresses (see DE19734055.5, DE19810929.6, and DE19709124.5). The disclosed methods share the following disadvantages: 1) catalysts used are expensive so as to result in excessive high production cost when said catalysts are used in industrial scale production, so that said methods have no advantage in comparison with the current production techniques. For example, tetraalkyl ammonium hydroxide and fluoride used in condensation reaction and noble metal, such as palladium, platinum, rhodium, and the like, used in hydrogenation reaction are expensive. The instability of tetraalkyl ammonium hydroxide imparts some difficulty to recovery and reuse of tetraalkyl ammonium hydroxide. The use of noble metal hydrogenation catalysts applies higher requirements to raw materials and equipments; 2) the yield is relatively low, and only suitable for laboratory research. This is an important reason why said methods are very difficult to be industrialized; 3) operation is complicated, and this isn't in favor of continuous operation and limits the production scale; 4) separation is difficult and purity of product is not high.

[0005] U.S. Pat. No. 6,395,933 discloses a process for synthesizing 4-aminodiphenylamine by reacting nitrobenzene and a substituted aniline at a certain temperature in the presence of a strong base and a phase-transfer catalyst. The process is unsatisfactory in yield and there are many side reactions. In the mixture of 4-nitrodiphenylamine and 4-nitrosodiphenylamine produced, the proportion of 4-nitrodiphenylamine is too high so that too much hydrogen is consumed during hydrogenation reaction and the production cost is thereby increased. Furthermore, said process needs an oxidizing agent so that it is not suitable for industrial production.

[0006] WO9300324 discloses a process for preparing 4-aminodiphenylamine by reacting nitrobenzene and aniline at a proper temperature in a proper solvent in the presence of a base with the content of proton materials in solution being controlled. Said process requires a solvent and has to control the content of proton materials in solution. The introduction of the solvent results in the increment of energy consumption and separation difficulty. Controlling the content of proton materials gives rise to difficulty of operating and controlling the reaction. In particular, at the later stage of condensation reaction, controlling the content of proton materials in the solution, which mainly means dehydrating to a lower water content, will prolong reaction time and partial aniline will be entrained out. The later stage, the more difficult removing the proton materials. Controlling the proton materials at a certain level is difficult, and goes against industrial production. The expensive tetraalkyl quaternary amine base catalyst will quickly decompose in the course of controlling the content of proton materials to a range of from 0.5 to 4 percent, resulting in the increment of the production cost.

SUMMARY OF THE INVENTION

[0007] The invention aims at the selection of inexpensive catalysts with good performance used for condensation and hydrogenation reactions and at the selection of a process suitable for industrial scale production, to continuously produce 4-aminodiphenylamine.

[0008] The present invention utilizes a complex base catalyst as condensation catalyst and a conventional hydrogenation catalyst or a powdery composite catalyst as hydrogenation catalyst, to prepare 4-aminodiphenylamine in a continuous process comprising five process stages of condensation; separation I (separating, recovering and reusing the complex base catalyst); hydrogenation; separation II (separating, recovering and reusing aniline, optionally separating, recovering and reusing hydrogenation solvent, and if necessary, separating, recovering and reusing hydrogenation catalyst which is optionally at least partially regenerated); and refining.

BRIEF DESCRIPTION OF THE FIGURE

[0009] FIG. 1 is a flowchart showing an embodiment of the process for preparing 4-aminodiphenylamine according to the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0010] According to an embodiment of the present invention, a process for preparing 4-aminodiphenylamine is provided, which process comprises five process stages: condensation; separation I, i.e. separating, recovering and reusing complex base catalyst; hydrogenation; separation II, i.e. separating, recovering and reusing aniline and optionally separating, recovering and reusing hydrogenation solvent, and if necessary, separating, recovering and reusing the hydrogenation catalyst which is optionally at least partially regenerated; and refining, and uses nitrobenzene and aniline as raw materials and a complex base catalyst as condensation catalyst.

[0011] In another embodiment according to the present invention, hydrogenation catalyst used in the hydrogenation reaction is selected from the group consisting of conventional hydrogenation catalysts comprising Group VIII element(s) of the Periodic Table or Cu, Cr, Zn or Mn as active component and/or co-catalyst component or powdery composite catalysts.

[0012] In still another embodiment according to the present invention, the powdery composite catalyst comprises nickel, aluminum and component A, said component A being at least one selected from the group consisting of Fe, Cu, Co, Mn, Cr, Mo, B and P, and wherein the content of nickel ranges from 25 to 99.9 wt.-%, and the total content of aluminum and component A ranges from 0.1 to 75 wt.-%.

[0013] In still another embodiment according to the present invention, the condensation reaction is carried out under conditions of a molar ratio of nitrobenzene to aniline of from 1:1 to 1:15, a reaction temperature of from 20 to 150° C., a reaction pressure of from 0.005 to 0.1 MPa (absolute pressure) and a reaction time of from 3.5 to 6 h.

[0014] In still another embodiment according to the present invention, in separation I, the complex base catalyst is recovered by neutralizing the reaction system with an acidic matter to conduct separation, then basifying aqueous phase using a base, wherein said acidic matter is selected from the group consisting of inorganic acids, combinations of oxides thereof and-water, and inorganic acid-form salts, preferably hydrochloric acid, sulfuric acid, nitric acid, carbonic acid, sodium bicarbonate, a combination of carbon dioxide and water, a combination of sulfur trioxide and water; said base is selected from the group consisting of hydroxides or oxides of alkali metals and alkaline earth metals, and the acidic matter and the base are chosen according to type of tetraalkyl ammonium salt and base in the complex base catalyst.

[0015] In still another embodiment according to the present invention, molar ratio of hydroxide ion in the complex base catalyst to nitrobenzene is in a range of from 1:4 to 4:1.

[0016] In still another embodiment according to the present invention, the complex base catalyst used in the condensation reaction comprises a tetraalkyl ammonium hydroxide, an alkali metal hydroxide, and a tetraalkyl ammonium salt.

[0017] In still another embodiment according to the present invention, molar ratio of tetraalkyl ammonium hydroxide to alkali metal hydroxide to tetraalkyl ammonium salt in the complex base catalyst equals (0-9):(0.5-3):(0.5-3), and the sum of concentration of tetraalkyl ammonium hydroxide, alkali metal hydroxide and tetraalkyl ammonium salt ranges from 10 to 100 percent by weight.

[0018] In still another embodiment according to the present invention, the used complex base catalyst is prepared as follows: tetraalkyl ammonium hydroxide, alkali metal hydroxide or oxide and tetraalkyl ammonium salt, at desired molar ratio, are stirred in water at a temperature of from 0 to 90° C. until being homogeneous, to form an aqueous form of the complex base catalysts, said tetraalkyl ammonium hydroxide, alkali metal hydroxide or oxide and tetraalkyl ammonium salt as raw materials being in solid form or in aqueous solution form.

[0019] In still another embodiment according to the present invention, the used complex base catalyst is prepared as follows: tetraalkyl ammonium hydroxide, alkali metal hydroxide or oxide and tetraalkyl ammonium salt, at desired molar ratio, are stirred in water at a temperature of from 0 to 90° C. until being homogeneous, then water is completely removed through azeotropic process by adding benzene, to form an anhydrous form of the complex base catalysts, said tetraalkyl ammonium hydroxide, alkali metal hydroxide or oxide and tetraalkyl ammonium salt as raw materials being in solid form or in aqueous solution form.

[0020] In still another embodiment according to the present invention, the tetraalkyl ammonium salt is represented by a general formula of

$$[(R1)(R2)(R3)(R4)N]^{+}{}_{n}X^{n-}$$

[0021] wherein R1, R2, R3 and R4, which may be identical or different, can be alkyl having from 1 to 4 carbon atoms, said alkyl being optionally substituted by a hydrophilic substituent; X^{n-} is selected from the group consisting of halide ion, sulfate radical, carbonate radical, phosphate radical, bicarbonate radical, bisulfate radical, C_1-C_2-alkyl carbonate radical, C_1-C_2-alkyl sulfate radical, etc.; and n is a value of from 1 to 2.

[0022] In still another embodiment according to the present invention, in said general formula of the tetraalkyl ammonium salt, at least one of R1, R2, R3 and R4 is substituted by a hydrophilic substituent selected from the group consisting of hydroxy, methoxy, polyether, cationic polyamide, polyester, polyethylene polyamine and highly water-soluble quaternary ammonium salt-containing radical.

[0023] In still another embodiment according to the present invention, the tetraalkyl ammonium salt is a hydrophilic substituent-carring tetraalkyl ammonium salt selected from the group consisting of poly-methylated triethylene tetraamine sulfate, poly-methylated diethylene triamine carbonate, N,N-dimethyl-N,N-bis(methoxyethyl) ammonium carbonate, N-methyl-N,N,N-tri(methoxyethyl) ammonium carbonate, N,N,N-trimethyl-N-hydroxyethyl ammonium carbonate, trimethyl hydroxyethyl ammonium chloride, N,N,N-trimethyl-N-ethoxylated (1-4 moles of ethylene oxide) ethyl ammonium carbonate, N,N,N-trimethyl-N-ethoxylated (1-4 moles of ethylene oxide) propyl ammonium carbonate, N,N,N-trimethyl-N-ethoxylated (1-4 moles of ethylene oxide) propyl ammonium chloride, N,N-dimethyl-N,N-bis(ethoxylated (1-4 moles of ethylene oxide) propyl) ammonium carbonate.

[0024] In still another embodiment according to the present invention, the tetraalkyl ammonium salt is selected from the group consisting of tetramethyl ammonium carbonate, tetramethyl ammonium methyl-carbonate, tetraethyl ammonium carbonate, tetraethyl ammonium ethyl-carbonate, tetramethyl ammonium sulfate, tetramethyl ammonium methyl-sulfate, tetraethyl ammonium sulfate, and tetraethyl ammonium ethyl-sulfate.

[0025] In still another embodiment according to the present invention, the tetraalkyl ammonium salt is those prepared by reacting trialkyl amine with di(C_1-C_2)alkyl carbonate or di(C_1-C_2)alkyl sulfate in polar solvent.

[0026] In still another embodiment according to the present invention, the reaction for the preparation of the tetraalkyl ammonium salt is carried out under the following conditions: reaction pressure ranges from 0.1 to 3.0 MPa, reaction temperature ranges from 50-200° C., reaction time ranges from 1.5 to 6 h, molar ratio of trialkyl amine to di(C_1-C_2)alkyl carbonate or di(C_1-C_2)alkyl sulfate ranges from 2:1 to 1:2, the polar solvent used is methanol, ethanol or isopropanol, and the polar solvent is used in an amount of from 1 to 10 times of weight of the trialkyl amine.

[0027] In still another embodiment according to the present invention, the condensation reaction is carried out in the absence of oxygen.

[0028] In still another embodiment according to the present invention, it is not necessary to add additionally or control proton materials during the condensation reaction.

[0029] In still another embodiment according to the present invention, the condensation reaction is carried out without a solvent.

[0030] In still another embodiment according to the present invention, an amount of complex base catalyst is added during initial stage of the condensation reaction and only tetraalkyl ammonium salt component and/or alkali metal hydroxide or oxide component of the complex base catalyst are replenished in the course of the reaction.

[0031] In still another embodiment according to the present invention, the condensation process stage is conducted in a circulating system consisting of a condensing circulating pump, a falling film reactor and a first reactor, and optional subsequent-reactor(s).

[0032] In still another embodiment according to the present invention, a falling film reactor is used in the condensation process stage and the falling film reactor utilizes ethanol vapor, hot water, steam or methanol vapor as heat medium.

[0033] In still another embodiment according to the present invention, the hydrogenation reaction is carried out under the following conditions: hydrogen gas is used as reducing agent; volume ratio of gas to liquid is in a range of from 10:1 to 1500:1, weight ratio of solid to liquid is in a range of from 0.5:100 to 16:100 when non-fixed bed hydrogenation process is used, and weight ratio of solvent to separation I liquid (i.e., condensation liquid from which the complex base catalyst has been separated) is in a range of from 1:10 to 5:10, with the gas representing hydrogen gas, the liquid including solvent and separation I liquid, and the solid representing hydrogenation catalyst; the temperature of hydrogenation reaction ranges from 50 to 150° C., the pressure of the reactor ranges from 0.2 to 6.0 MPa (absolute pressure), and the reaction time ranges from 2 to 7 h.

[0034] In still another embodiment according to the present invention, the powdery composite catalyst used in the hydrogenation reaction is prepared by mixing powdery nickel, powdery aluminum and component A in desired proportion, then melting them at high temperature, followed by pulverizing them into powder after discharging and quenching, and then treating the powder with an aqueous solution of a hydroxide.

[0035] In still another embodiment according to the present invention, a magnetic separator is used to recover magnetic powdery composite catalyst after the hydrogenation reaction.

[0036] In still another embodiment according to the present invention, recovered powdery composite catalyst is conveyed back to the hydrogenation reactor via a Venturi type mixed solid-liquid conveying equipment utilizing feeding power.

[0037] In still another embodiment according to the present invention, deactivated powdery composite catalyst is regenerated by treating with ultrasonic vibration and/or strong base.

[0038] In still another embodiment according to the present invention, the solvent used in the hydrogenation reaction is an alcohol and/or water.

[0039] In still another embodiment according to the present invention, the refining is performed through three-column continuous rectification plus batch rectification process, and wherein rectification column 1, rectification column 2 and rectification column 3 are operated at a vacuum degree ranging independently from 0.09 to 0.098 MPa; a still temperature of from 260 to 290° C., from 260 to 300° C. and from 120 to 170° C., respectively; a reflux ratio of from 2:1 to 10:1, from 1:0.5 to 1:4 and from 1:0.5 to 1:2, respectively; and the batch rectification column is operated

at a vacuum degree of from 0.09 to 0.098 MPa, and a still temperature of from 280 to 330° C.

[0040] In the process according to the present invention, "separation I" means separating, recovering and reusing complex base catalyst; and "separation II" means separating, recovering and reusing aniline and optionally separating, recovering and reusing hydrogenation solvent, and if necessary, separating, recovering and reusing hydrogenation catalyst which is optionally at least partially regenerated. The expression "optionally separating, recovering and reusing hydrogenation solvent" as used herein intends to means that, when water is used as hydrogenation solvent, the water is optionally recovered and reused, and when an alcohol solvent, which will be described hereinbelow, is used as hydrogenation solvent, the alcohol hydrogenation solvent is separated, recovered and reused.

[0041] With reference to the FIG. 1, in a preferred embodiment according to the present invention, the process for preparing 4-aminodiphenylamine according to the present invention comprises the steps of:

[0042] continuously feeding nitrobenzene, aniline and a complex base catalyst, at desired proportion, to condensation process stage via metering pumps, and allowing them to react to form a condensation liquid (7) containing 4-nitrodiphenylamine, 4-nitrosodiphenylamine and/or salts thereof;

[0043] continuously feeding the condensation liquid (7) to separation I process stage, where the complex base catalyst is recovered by neutralizing the condensation liquid (7) with an acidic matter to conduct separation, then basifying aqueous phase using a base, and then the recovered complex base catalyst (1) is recycled back to the condensation process stage;

[0044] continuously feeding separation I liquid (i.e., the condensation liquid from which the complex base catalyst has been separated) (8), hydrogenation solvent, including supplementary hydrogenation solvent (3) and optionally recovered hydrogenation solvent (5), at desired proportion to hydrogenation process stage, and allowing them to react with hydrogen gas under the catalytic action of a powdery composite catalyst, including supplementary powdery composite catalyst (2) and reused, optionally at least partially regenerated, powdery composite catalyst (4), to form a hydrogenation liquid (9) containing 4-aminodiphenylamine;

[0045] feeding the hydrogenation liquid (9) to separation II process stage, where (a) powdery composite catalyst (4), which is to be recycled back to the hydrogenation process stage directly or after being at least partially regenerated, (b) aniline (6), which is to be recycled back to the condensation process stage, and (c) optionally, hydrogenation solvent (5), which is to be recycled back to the hydrogenation process stage, are obtained; and feeding crude 4-aminodiphenylamine (10), from which most of aniline has been separated, to refining process stage, where (a) partial aniline (6), which is to be recycled back to the condensation process stage, and (b) the finished 4-aminodiphenylamine are obtained. The whole process is conducted continuously.

[0046] In the condensation reaction, molar ratio of nitrobenzene to aniline is in a range of from 1:1 to 1:15; reaction temperature may be in a range of from 20 to 150° C., preferably from 50 to 90° C., and controlling the reaction temperature not higher than 90° C. can result in a decomposition ratio of the complex base catalyst of less than 0.5 percent during the condensation; reaction pressure may vary from 0.005 to 0.1 MPa (absolute pressure); and residence time of the stuff in the whole condensation reaction system is in a range of from 3.5 to 6 h.

[0047] The complex base catalyst used in the condensation reaction comprises a tetraalkyl ammonium hydroxide, an alkali metal hydroxide, a tetraalkyl ammonium salt and optional water, wherein the concentration sum of tetraalkyl ammonium hydroxide, alkali metal hydroxide and tetraalkyl ammonium salt is in a range of from 10 to 100 percent by weight, preferably from 25 to 38 percent by weight, and wherein the molar ratio of tetraalkyl ammonium hydroxide to alkali metal hydroxide to tetraalkyl ammonium salt is (0-9):(0.5-3):(0.5-3). The combination of part tetraalkyl ammonium hydroxide and inexpensive alkali metal hydroxide or oxide and tetraalkyl ammonium salt can attain the same object as attained in the prior art where highly pure tetraalkyl ammonium hydroxide is used as catalyst. In the condensation reaction mixture, the molar ratio of hydroxide ion in complex base catalyst to nitrobenzene is in a range of from 1:4 to 4:1.

[0048] The complex base catalysts used for the condensation reaction is prepared as follows: tetraalkyl ammonium hydroxide, alkali metal hydroxide or oxide and tetraalkyl ammonium salt, at a molar ratio of (0-9):(0.5-3):(0.5-3), are stirred in water at a temperature of from 0 to 90° C. until being homogeneous, to form an aqueous form of the complex base catalysts. Then water can be completely removed by adding benzene through azeotropic process, to form an anhydrous form of the complex base catalysts. Said tetraalkyl ammonium hydroxide, alkali metal hydroxide or oxide and tetraalkyl ammonium salt as raw materials can be in solid form or in aqueous solution form.

[0049] In the course of industrial production, the reaction mixture unavoidably contacts with carbon dioxide and carbon monoxide in ambient air and hydrogen, so that the tetraalkyl ammonium hydroxide will decrease in amount by converting to tetraalkyl ammonium carbonate. In the case where only a tetraalkyl ammonium hydroxide is used as catalyst, the transformation of tetraalkyl ammonium hydroxide into ammonium salt will decrease the quantity of the catalyst, so that there need supply the catalyst and get rid of the ammonium salt. In contrast, with the complex base catalyst according to the present invention, there needs no any complex technology but increasing the content of alkali metal hydroxide or oxide in the complex base catalyst.

[0050] According to the present invention, nitrobenzene and aniline are condensed to form 4-nitrodiphenylamine and 4-nitrosodiphenylamine and/or their salts at certain conditions using the complex base catalyst. Anhydrous form of the complex base catalyst may be used to convert nitrobenzene and aniline to 4-nitrodiphenylamine and 4-nitrosodiphenylamine and/or their salts in the condensation reaction according to the present invention. The selectivity and conversion of the reaction attain to the desired level at an anhydrous condition.

[0051] In the case of using a complex base catalyst, it is possible not to severely control proton materials such as water, methanol and the like, thereby avoiding as much as possible the loss of the complex base catalyst and operation complexity caused by the control of proton materials. Without limited to any specific theory, it is believed that the integrated action of tetraalkyl ammonium hydroxide, alkali hydroxide and tetraalkyl ammonium salt in the complex base catalyst gives rise to such a result, thereby reducing the difficulty of operating and controlling the reaction. It is believed that the use of the complex base catalyst comprising tetraalkyl ammonium hydroxide, alkali hydroxide and tetraalkyl ammonium salt makes the control of proton materials, for example, water in reaction system unimportant. That is to say, condensation reaction can be carried out with the conversion and selectivity being not affected no matter whether there are no proton materials such as water in the solution or there is a high content of proton materials such as water in the solution. Thus, the difficulty of operating and controlling the reaction can be reduced and the quantity of aniline entrained out by azeotropic dehydration can be decreased, so that the process is more suitable for industrial scale production.

[0052] In the process according to the present invention, proton materials such as water no longer construct a restricting factor of the reaction, and the selectivity and conversion can attain to the desired level whether or not there are proton materials such as water. Furthermore, it has been found that the decomposition rate of the complex base catalyst is lower than that of the single tetraalkyl ammonium hydroxide.

[0053] In a preferred embodiment of the present invention, condensation reaction can be carried out as follows: nitrobenzene, aniline and complex base catalyst, at desired proportion, are continuously fed via metering pumps to a falling film reactor to be heated and allowed to condense; the condensation liquid in the falling film reactor is discharged from the bottom of the reactor into a first reactor to continue condensation reaction; a part of the condensation liquid from the bottom of the first reactor is conveyed back to the falling film reactor via a circulating pump, to establish a local circulating system of the condensation reaction according to the present invention. The circulating system mainly consists of the falling film reactor and the first reactor, and reactants continuously circulate in said circulating system via the condensation circulating pump. The circulating process maintains an amount of condensation liquid sufficient to form a uniform film in the falling film reactor. The falling film reactor may utilize ethanol vapor, hot water, steam or methanol vapor, preferably ethanol vapor as heat medium, to make the temperature of the system very homogeneous and avoid local overheating. That there is hardly back-mixing of reaction liquid in a falling film reactor significantly decreases the contact chance of product and raw materials and minimizes the side reaction. The local circulating system including the falling film reactor enhances the condensation reaction rate and reduces the reaction time, which is shortened from more than ten hours to 3.5-6 hours.

[0054] It has also been found that continuous film reaction is higher than complete mixing reaction in both selectivity and yield. During this reaction, nitrobenzene reacts with aniline to form 4-nitrosodiphenylamine; nitrobenzene can also react with 4-nitrosodiphenylamine to form 4-nitrodiphenylamine, and nitrobenzene itself is reduced to nitrosobenzene, which in turn can react with aniline to form azobenzene. The latter reaction goes against main reaction and reduces the selectivity of the reaction. At the beginning of reaction, the quantity of nitrobenzene is relatively bigger. Nitrobenzene is gradually converted to 4-nitrosodiphenylamine and the quantity of nitrobenzene becomes smaller along with the reaction. The use of the continuous film reactor reduces the contact and reaction between nitrobenzene added and 4-nitrosodiphenylamine which is later formed (when the reactants enter the reactor to react, the concentration of nitrobenzene is relatively higher yet the concentration of 4-nitrosodiphenylamine is relatively lower, while at the end of the reaction, the concentration of 4-nitrosodiphenylamine is relatively higher yet the concentration of nitrobenzene is relatively lower), that is, the opportunity that nitrobenzene is reduced to nitrosobenzene by 4-nitrosodiphenylamine, thereby reducing reaction between nitrobenzene and aniline to form azobenzene.

[0055] In the condensation reaction of nitrobenzene and aniline in the presence of the complex base catalyst, the main side reaction is to form by-products, azobenzene and phenazine. It has been found that the bigger the quantity of aniline, the less the side reaction to convert nitrobenzene to phenazine. Another by-product in the reaction is azobenzene. Azobenzene can be easily transformed into aniline at the hydrogenation process stage, so that it can be reused in the production. Therefore, the molar ratio of nitrobenzene to aniline employed in the invention is selected as from 1:1 to 1:15.

[0056] Furthermore, in the process according to the present invention, condensation reaction can be performed under proper ratio of nitrobenzene and aniline without the introduction of any solvent into the system and a good yield can be achieved.

[0057] The invention improves the yield of the condensation reaction and makes the reaction moving towards desired direction utilizing the above method.

[0058] Those skilled in the art can contemplate that the condensation reaction according to the present process might employ more stages of reactors in series.

[0059] In the condensation process stage, it is unavoidable to lose part of complex base catalyst used in condensation process along with the reaction. It is possible to supply only alkali metal hydroxide component and tetraalkyl ammonium salt component of the complex base catalyst when replenishing the catalyst, and their molar ratio is in a range of from 4:1 to 1:4. Alkali metal oxide can be used to replace alkali metal hydroxide, and its amount can be gotten by conversion from corresponding hydroxide.

[0060] The tetraalkyl ammonium salts useful in the present invention can be represented by a general formula of

$$[(R1)(R2)(R3)(R4)N]^{+}_{n}X^{n-}$$

[0061] wherein R1, R2, R3 and R4, which may be identical or different, can be alkyl having from 1 to 4 carbon atoms, said alkyl can carry a hydrophilic substituent selected from the group consisting of hydroxy, methoxy, polyether, cationic polyamide, polyester, polyethylene polyamine, highly water-soluble quaternary ammonium salt-containing radical, etc., X^{n-} is selected from the group consisting of halide ions, sulfate radical, carbonate radical, phosphate

radical, bicarbonate radical, bisulfate radical, C_1-C_2-alkyl carbonate radical, C_1-C_2-alkyl sulfate radical, etc., and n is a value of from 1 to 2. Examples of the tetraalkyl ammonium salts include, but are not limited to, poly-methylated triethylene tetraamine sulfate, poly-methylated diethylene triamine carbonate, N,N-dimethyl-N,N-bis(methoxyethyl) ammonium carbonate, N-methyl-N,N,N-tri(methoxyethyl) ammonium carbonate, N,N,N-trimethyl-N-hydroxyethyl ammonium carbonate, trimethyl hydroxyethyl ammonium chloride, N,N,N-trimethyl-N-ethoxylated (1-4 moles of ethylene oxide) ethyl ammonium carbonate, N,N,N-trimethyl-N-ethoxylated (1-4 moles of ethylene oxide) propyl ammonium carbonate, N,N,N-trimethyl-N-ethoxylated (1-4 moles of ethylene oxide) propyl ammonium chloride, N,N-dimethyl-N,N-bis(ethoxylated (1-4 moles of ethylene oxide) propyl) ammonium carbonate, tetramethyl ammonium carbonate, tetramethyl ammonium methyl-carbonate, tetraethyl ammonium carbonate, tetraethyl ammonium ethyl-carbonate, tetramethyl ammonium sulfate, tetramethyl ammonium methyl-sulfate, tetraethyl ammonium sulfate, and tetraethyl ammonium ethyl-sulfate.

[0062] The tetraalkyl ammonium hydroxides used in the complex base catalyst can be represented by a formula of $R'_4N^+OH^-$, wherein R' is independently an alkyl having one or two carbon atoms. The tetraalkyl ammonium hydroxide may be prepared from corresponding tetraalkyl ammonium salt and base in polar solvent according to a process known per se.

[0063] The alkali metal hydroxides or oxides include hydroxides and oxides of lithium, sodium, potassium and rubidium, such as sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium oxide or potassium oxide.

[0064] The tetraalkyl ammonium alkyl-carbonates or tetraalkyl ammonium alkyl-sulfates useful in the present invention can be prepared by the reaction of trialkyl amine and di(C_1-C_2)alkyl carbonate or di(C_1-C_2)alkyl sulfate in polar solvent.

[0065] According to the present invention, in the preparation of tetraalkyl ammonium alkyl-carbonates or tetraalkyl ammonium alkyl-sulfates, the reaction temperature varies from 50 to 200° C., preferably from 60 to 150° C., and reaction pressure varies from 0.1 to 3 MPa (gauge pressure). In general, the pressure depends on the selected temperature, as well as type and amount of the solvent, namely, the less the amount of solvent, the higher the system pressure; and the higher the temperature, the higher the pressure. In the present invention, the reaction pressure is preferably controlled in a range of from 0.4 to 2 MPa to obtain higher product yield.

[0066] In the reaction for the preparation of tetraalkyl ammonium alkyl-carbonate or tetraalkyl ammonium alkyl-sulfate according to the present invention, the molar ratio of trialkyl amine to di(C_1-C_2)alkyl carbonate or di(C_1-C_2)alkyl sulfate is chosen as from 2:1 to 1:2. If the proportion of trialkyl amine is too high, then trialkyl amine will be superabundant in the reaction system and thus impose operational difficulty to subsequent processes and pollutes the environment. If the proportion of trialkyl amine is too low, then di(C_1-C_2)alkyl carbonate or di(C_1-C_2)alkyl sulfate will be superabundant, resulting in the loss of di(C_1-C_2)alkyl carbonate or di(C_1-C_2)alkyl sulfate in the subsequent reaction, thereby increasing the production cost.

[0067] In the process for the preparation of tetraalkyl ammonium alkyl-carbonate or tetraalkyl ammonium alkyl-sulfate according to the present invention, reaction time of trialkyl amine and di(C_1-C_2)alkyl carbonate or di(C_1-C_2)alkyl sulfate is in a range of from 1.5 to 6 h. At the initial stage of the reaction, the reaction rate is high, and exothermic phenomenon is obvious. With consumption of raw materials, the reaction became slow and heat release is gradually reduced. During the reaction, the amount of cooling water is continuously adjusted to keep reaction temperature and pressure in a certain range.

[0068] The polar solvents useful in the reaction for the preparation of tetraalkyl ammonium alkyl-carbonate or tetraalkyl ammonium alkyl-sulfate according to the present invention include methanol, ethanol or isopropyl alcohol. The amount of solvents used varies from 1 to 10 times of weight of trialkyl amine.

[0069] In separation I process stage, the condensation liquid containing 4-nitrodiphenylamine and 4-nitrosodiphenylamine and/or salts thereof is filtered, and an acidic matter is added to the filtrate to reduce pH of the solution to about 8, then layers are separated. The obtained organic phase is a mixture of 4-nitrodiphenylamine and 4-nitrosodiphenylamine, i.e. separation I liquid. A base is added to the obtained aqueous phase at such an amount that equivalent ratio of the base to above-added acidic matter is in a range of from 1:1 to 3:1, to give the complex base catalyst. If necessary, the recovered complex base catalyst may be concentrated prior to being recycled back to the condensation process stage.

[0070] The acidic matters useful in the separation I process stage may be selected from the group consisting of inorganic acids, combinations of oxides thereof and water, and inorganic acid-form salts, for example, hydrochloric acid, sulfuric acid, nitric acid, carbonic acid, sodium bicarbonate, a combination of carbon dioxide and water, a combination of sulfur trioxide and water, and the like; and the base used may be selected from the group consisting of hydroxides or oxides of alkali metals and alkaline earth metals. It is desired to choose suitable acidic matter and base based on the type of the tetraalkyl ammonium salt and the base in the complex base catalyst. The principles for making such a choice are well known by ordinarily skilled persons in the art. For example, if tetraalkyl ammonium salt is a chloride, hydrochloride acid is chosen as the acidic matter in order to avoid to introduce other impurities. For another example, if tetraalkyl ammonium salt is a carbonate, then a combination of carbon dioxide and water can be used to neutralize the filtrate, and calcium hydroxide is used to basify the aqueous phase.

[0071] It should be pointed out that the present invention avoids the problem that the complex base catalysts thermally decompose in the hydrogenation reaction by separating the complex base catalysts from 4-nitrodiphenylamine and 4-nitrosodiphenylamine in separation I process stage utilizing an acidic matter, thereby largely enlarging the selectable range of hydrogenation catalyst. The hydrogenation catalysts useful in the hydrogenation reaction according to the present invention may be any conventional hydrogenation catalyst comprising Group VIII element(s) of the Periodic Table or Cu, Cr, Zn, Mn etc. as active component and/or co-catalyst component or a powdery composite catalyst. The tempera-

ture of hydrogenation reaction may range from 50 to 150° C., and the hydrogenation reactor may employ one-stage or multi-stage of fluidized bed reactor(s), or one-stage or multi-stage of fixed bed reactor(s) in series. If a catalyst in a form suitable for fixed bed reactor, for example, granular catalyst, is used, the process may be adjusted in a manner well known by those skilled in the art, for example, there needs not filter the hydrogenation catalyst in separation II process staged described hereinbelow, and there needs not recover hydrogenation catalyst using a magnetic separator in the hydrogenation process. These embodiments are also encompassed in the present invention.

[0072] Now hydrogenation and separation II process stages of the process according to the present invention in which a powdery composite catalyst of the present invention as well as fluidized bed hydrogenation process is employed are described.

[0073] In the hydrogenation reaction of said embodiment of the present invention, hydrogen gas can be used as reducing agent. The reaction temperature is in a range of from 50 to 150° C., the pressure is in a range of from 0.2 to 6.0 MPa (absolute pressure), and the reaction time varies from 2 to 7 h. Volume ratio of gas to liquid is in a range of from 10:1 to 1500:1, weight ratio of solid to liquid is in a range of from 0.5:100 to 16:100, with the gas representing hydrogen gas, the liquid including hydrogenation solvent and separation I liquid, and the solid representing powdery composite catalyst.

[0074] In the practice of the invention, alcohols and/or water can be used as hydrogenation solvent. As alcohols, methanol, ethanol and isopropyl alcohol are preferred. The hydrogenation solvent can be used in such an amount that weight ratio of hydrogenation solvent to separation I liquid is in a range of from 1:10 to 5:10.

[0075] The powdery composite catalysts useful in the hydrogenation reaction according to the present invention comprise nickel, aluminum and component A which is at least one selected from the group consisting of Fe, Cu, Co, Mn, Cr, Mo, B and P, wherein the content of nickel is in a range of from 25 to 99.9 wt.-%, and the total content of aluminum and component A is in a range of from 0.1 to 75 wt.-%. The particle size of the catalysts may vary from 40 to 300 mesh.

[0076] The modifying agent A, which is at least one selected from the group consisting of Fe, Cu, Co, Mn, Cr, Mo, B and P, can modify the crystalline state of nickel-aluminum alloy so as to achieve the purpose of improving the selectivity of hydrogenation reaction and enhancing the activity of catalyst. The powdery composite catalysts according to the present invention can be prepared by mixing powdery nickel, powdery aluminum and component A at desired proportion, then melting them at high temperature, followed by pulverizing them into powder with a particle size ranging from 40 to 300 mesh after discharging and quenching, and finally, treating the powder with hydroxide aqueous solution. The concentration of hydroxide solution can be in a range of from 5 to 50 weight percent, and the treating temperature is in a range of from 50 to 90° C.

[0077] In order to improve the effect of recovering hydrogenation catalysts by magnetic separator in the subsequent process, it is preferred to use at least iron as modifying agent to increase the ferromagnetism of the powdery composite catalysts. Therefore, in a preferred embodiment of the present invention, the powdery composite catalysts according to the present invention can be prepared by taking powdery nickel, powdery aluminum, powdery iron, and optional other modifying agent A, which is selected from the group consisting of Cu, Cr, Co, Mn, Mo, B and P, in desired proportion; melting them into alloy in an induction furnace; ejecting the molten alloy using gas pressure through a nozzle to a copper drum rotating at high speed to quench quickly the alloy with cooling speed being as high as 10^5-10^6 K/sec; pulverizing the cooled alloy using a ball mill into powder with a particle size ranging from 40 to 300 mesh, preferably from 100 to 200 mesh; and finally, treating the powder with 5 to 50 wt.-% aqueous solution of a hydroxide at a temperature of from 50 to 90° C.

[0078] According to a preferred embodiment of the invention, hydrogenation reaction can be carried out as follows: separation I liquid, hydrogenation solvent, powdery composite catalyst recovered and, if necessary, complementary fresh powdery composite catalyst are fed to first-stage, second-stage and optional higher-stage hydrogenation reactors via a solid-liquid conveyer, and hydrogen gas is bubbled into the reactors from bottom of the reactors via a hydrogen gas circulator, to carry out the hydrogenation reaction under the above-defined hydrogenation reaction conditions to form crude hydrogenation liquid containing 4-aminodiphenylamine. The powdery composite catalyst entrained out by crude hydrogenation liquid is separated by a settling vessel and a magnetic separator. Solid-liquid phase, which separates from hydrogenation liquid and contains high concentration of the powdery composite catalyst, enters the first-stage reactor to be reused through a mixed solid-liquid conveying device. At the same time, hydrogenation liquid containing 4-aminodiphenylamine is obtained.

[0079] The powdery composite catalyst according to the present invention is a solid-state material during the hydrogenation. In industry, a hydrogenation catalyst is typically circulated via a pump, however, when a pump is used to convey a catalyst containing a high concentration of powdery metal, pump cavity is easily damaged and the transportation effect is also not good. The inventors design a Venturi-like solid-liquid conveying device, and circulation of the powdery composite catalyst in hydrogenation system is achieved through a pump-free circulation performed, by skillfully employing the power of the pump for feeding separation I liquid, so that the loss of catalyst is significantly reduced, and the concentration of catalyst in hydrogenation reaction mixture is significantly enhanced.

[0080] According to a preferred embodiment, in continuous hydrogenation process, the powdery composite catalyst in crude hydrogenation liquid is recovered through sedimentation and magnetic separator and recycled via a Venturi type solid-liquid conveying device, and circulating hydrogen gas is bubbled into the reactors. The whole hydrogenation step is conducted in a complete mixing flow mode by continuously feeding stock into multistage reactors in series. The hydrogenation solvents can be the recovered and reused.

[0081] The hydrogenation liquid having part of the powdery composite catalyst recovered through sedimentation and magnetic separator enters separation II process stage, where the residual powdery composite catalyst in the hydro-

genation liquid is recovered from hydrogenation liquid by filtration, and circulated back to the hydrogenation process stage directly or after being at least partially regenerated.

[0082] In the hydrogenation reaction according to the present invention, with optionally continuously renewing a minor amount of hydrogenation catalyst, the catalyst concentration in the reaction system can always maintain at a higher level. Such a method of recycling catalyst can always and stably maintain the total activity of catalyst in the system at a higher level and avoid the problem that catalyst activity gradually decreases suffered by the processes employing a fixed bed catalyst. The use of magnetic separator facilitates the recovery of the catalyst, and the designing and application of mixed solid-liquid conveying device make powdery composite catalyst circulating in the hydrogenation system.

[0083] In the present invention, deactivation of catalyst usually attributes to that inorganic matter or organic carbon deposition clog pores of the catalyst, so that the active sites of the catalyst are covered, and thereby the activity of the catalyst decreases. Therefore, the present invention employs washing with a high concentration base solution, for example, 5-50 wt.-% aqueous solution of alkali metal hydroxide in combination with ultrasonic vibration to regenerate the catalyst. Ultrasonic vibration facilitates to get rid of the inorganic deposition or organic carbon deposition, while the high concentration base solution can dissolve the aluminum, which isn't dissolved in the first base dissolution, in the catalyst to form new loose pore structures, thereby increasing the activity of the catalyst.

[0084] The inventors utilize sedimentation and magnetic separator to recover magnetic hydrogenation catalyst, and design a Venturi type mixed solid-liquid conveying device to convey the catalyst back to hydrogenation reactor using the power of feeding the stocks, thereby achieving the circulation of powdery composite catalyst. The inventors also take out the catalyst after filtration to regenerate it to restore its initial activity. By the two measures, the consumption of catalyst is significantly reduced, and the activity and lifetime of catalyst are improved.

[0085] In the separation II process stage, if the hydrogenation solvent used in the hydrogenation reaction is water, after filtering to recover the residual powdery composite catalyst, the layers of the hydrogenation liquid is separated, and the organic phase is continuously fed to aniline column, where aniline is obtained from the column top and recycled back to the condensation process stage, and crude 4-aminodiphenylamine is obtained from column bottom. If the hydrogenation solvent used in the hydrogenation reaction is a mixture of water and an alcohol, after filtering to recover the residual powdery composite catalyst, the layers of the hydrogenation liquid is separated, and aqueous phase and organic phase are respectively rectified to give the alcohol solvent and aniline, which are reused. If the hydrogenation solvent used in the hydrogenation reaction is an alcohol, after filtering to recover the residual powdery composite catalyst, the hydrogenation liquid is fed to a rectification column where the hydrogenation solvent is recovered from the column top and recycled back to the hydrogenation process, and the bottoms is fed to aniline column, where aniline is obtained from the column top and recycled back to the condensation process stage, and crude 4-aminodiphenylamine is obtained from column bottom. The aniline column can be operated at a pressure of from 0.005 to 0.1 MPa (absolute pressure), column bottom temperature is in a range of from 120 to 320° C., and the temperature of gas phase is in a range of from 60 to is 190° C.

[0086] The organic phase having most aniline separated in separation II process stage contains 4-aminodiphenylamine, aniline, azobenzene and phenazine, etc. In an embodiment of the present invention, the refining process is conducted through three-column continuous rectification plus batch rectification, wherein the organic phase to be refined is conveyed via a pump into rectification column 1, where aniline, azobenzene and phenazine are taken out from the column top, and crude 4-aminodiphenylamine is discharged from the column bottom. The effluent from the top of rectification column 1 enters rectification column 3, where aniline with a purity of about 99% is distilled from the top of rectification column 3 and can be directly recycled back to condensation process, and azobenzene and phenazine are left in the column bottom. Bottoms of rectification column 1 are conveyed via a pump to rectification column 2, where the finished 4-aminodiphenylamine is distilled from the top of rectification column 2, and bottoms of rectification column 2, after accumulating to a certain amount, are conveyed to batch still, where a minor amount of 4-aminodiphenylamine left in the bottoms is distilled off and conveyed back to rectification column 2, and the other residues are discharged from the still bottom.

[0087] In the above refining process according to the present invention, the rectification column 1 is operated at a vacuum degree of from 0.09 to 0.098 MPa, a reflux ratio of from 2:1 to 10:1, a column top temperature of from 80 to 130° C., and a still temperature of from 260 to 290° C.; the rectification column 2 is operated at a vacuum degree of from 0.09 to 0.098 MPa, a reflux ratio of from 1:0.5 to 1:4, a column top temperature of from 140 to 190° C., and a still temperature of from 260 to 300° C.; the rectification column 3 is operated at a vacuum degree of from 0.09 to 0.098 MPa, a reflux ratio of from 1:0.5 to 1:2, a column top temperature of from 80 to 120° C., and a still temperature of from 120 to 170° C.; and the batch rectification column is operated at a vacuum degree of from 0.09 to 0.098 MPa, a column top temperature of from 235-250° C., and a still temperature of from 280 to 330° C. The still temperature of the rectification column 2 is relatively lower, thus coking of 4-aminodiphenylamine can be reduced, and 96% or more of 4-aminodiphenylamine can be distilled off at the top of rectification column 2 operated at a relatively lower still temperature, so that the amount of 4-aminodiphenylamine in the bottoms to be subjected to batch distillation is significantly reduced.

[0088] The process for preparing 4-aminodiphenylamine according to the present invention uses nitrobenzene and aniline as raw materials, is continuously conducted in five process stages: condensation; separating the complex base catalyst; hydrogenation; separating aniline, hydrogenation solvent and the hydrogenation catalyst; and refining, and thus is suitable for industrial scale production. The use of the complex base catalysts in condensation process significantly decreases the difficulty of operating and controlling the reaction and renders the water in the reaction system being no longer a reaction-confining factor. The decomposition of complex base catalyst is much less than that of the single tetraalkyl ammonium hydroxide catalyst. The selection of a falling film reactor and raw material proportion improves

selectivity of the reaction. There needs no solvent. Selecting a complex base catalyst to catalyze the condensation reaction and separating it prior to the hydrogenation avoid the problem that the complex base catalysts thermally decompose in the hydrogenation reaction, largely enlarge the selectable range of hydrogenation catalysts so that it is possible to select cheaper hydrogenation catalyst to reduce cost, enlarge the temperature range suitable for hydrogenation reaction, make it possible to employ a fixed bed reactor filled with granular catalyst thereby reducing industrial technique difficulty of the hydrogenation reaction, and omitting the extraction step (separating the complex base catalyst from the organic phase using extractant and co-extractant) after hydrogenation. In the case where a powdery composite catalyst is used as hydrogenation catalyst, the hydrogenation catalyst is good at antitoxic performance, by-product is little, conversion and selectivity is high, a magnetic separator can be used to recover magnetic powdery composite catalyst during hydrogenation process; the hydrogenation catalyst is conveyed back to hydrogenation reactor via a Venturi type mixed solid-liquid conveying device using the power of feeding stocks; and catalyst can be regenerated by chemical and/or physical methods, and thus the consumption of catalyst is reduced. In the whole process, reaction conditions is mild, by-product is little, conversion and selectivity is high, the operational strength is low, no corrosive liquid is produced, and environment pollution is reduced. The purity of 4-aminodiphenylamine can exceed 99 wt.-%, and the yield in the whole industrial production process can be over 95%.

EXAMPLES

[0089] The following examples further describe the invention, but do not make limitation to the invention in any way.

Example 1

[0090] Preparation of a Complex Base Catalyst

[0091] To a 1000 ml three-necked flask equipped with a condenser and a stirrer were added 227.5 g of 20 wt.-% aqueous solution of tetramethyl ammonium hydroxide (0.5 mol), 10 g (0.25 mol) of sodium hydroxide and 346 g of 30 wt.-% aqueous solution of tetramethyl ammonium carbonate (0.5 mol). The mixture was homogeneously stirred at 72-77° C. to give a complex base catalyst having a concentration of 27.3 wt.-%.

Example 2

[0092] Preparation of a Powdery Composite Catalyst

[0093] 46 g of powdery nickel, 51 g of powdery aluminum, and 3 g of powdery iron were taken and mixed, then molten into alloy state in an induction furnace. The molten alloy was ejected using gas pressure through a nozzle to a copper drum rotating at high speed to be quenched quickly with cooling speed being as high as 10^5-10^6 K/sec. The cooled alloy was pulverized using a ball mill, and 99.7 g of powder with a particle size ranging from 40 to 300 mesh were obtained by sieving. 375 g of 20 wt.-% sodium hydroxide aqueous solution was charged into a 500 ml three-necked flask equipped with a thermometer and a stirrer, and the above powder was slowly added thereto. The mixture was stirred at 60° C. for 4 h, then the solid was washed with deionized water until neutral to give a powdery composite catalyst.

Example 3

[0094] A. Condensation

[0095] Under vacuum condition, feeding pumps for the above complex base catalyst, aniline and nitrobenzene were simultaneously switched on and adjusted to such flow rate as aniline 150 kg/h, nitrobenzene 30 kg/h and the complex base catalyst 200 kg/h. The aniline, nitrobenzene and complex base catalyst were continuously fed into a falling film reactor to be heated and allowed to condense. Condensation liquid in the falling film reactor was discharged from the bottom into a first reactor to proceed with condensing. Part of condensation liquid from the bottom of the first reactor was conveyed back to the falling film reactor via a circulating pump, forming a local circulating system. Ethanol vapor at 78-90° C. was used as the heat medium of the falling film reactor. Reaction temperature was controlled as 75° C., pressure was controlled as 0.008 MPa (absolute pressure) and flow rate of the circulating liquid was controlled as 1 m^3/h. The reactants overflowed from the first reactor into a second reactor. The process conditions of the second reactor, such as operational temperature and pressure, were identical with that of the first reactor. The total residence time of the reactants in the falling film reactor, first reactor and second reactor was controlled as 5 h. Once the condensation reaction became stable, the complex base catalyst recovered according to the procedure as described below could be used, with only a minor amount of fresh complex base catalyst prepared according to example 1 being replenished, and the molar ratio of hydroxide ion to nitrobenzene in the reaction mixture was controlled not less than 1:1. The effluent of the second reactor was found to contain not larger than 0.1 wt.-% of nitrobenzene, 24.9 wt.-% of water and 16.1 wt.-% of 4-nitrosodiphenylamine and 4-nitrodiphenylamine.

[0096] B. Separation I

[0097] Thus obtained condensation liquid was continuously fed into the separation I process stage. To the condensation liquid subjected to filtering were introduced carbon dioxide and water until pH of the solution reaches about 8. The layers of system were separated, then calcium hydroxide was added at a rate of 25 kg/h to the obtained aqueous phase. After filtering, the obtained complex base catalyst was concentrated to its initial concentration, then conveyed back to the condensation process. The obtained organic phase contained 4-nitrodiphenylamine and 4-nitrosodiphenylamine.

[0098] C. Hydrogenation

[0099] The organic phase containing 4-nitrodiphenylamine and 4-nitrosodiphenylamine obtained by filtration in the separation I was fed to a first-stage hydrogenation reactor equipped with a sealed magnetic stirrer and a cooling and heating system. Hydrogen gas was used to replace the atmosphere of the system and pressurize to 1.3 MPa. A hydrogen gas circulator was switched on and flow rate of circulating hydrogen gas was maintained at 1 Nm^3/h. The circulating hydrogen gas was bubbled into the hydrogenation reactors to improve the gas-liquid mass transfer effect during reaction. The flow rate of the organic phase containing 4-nitrodiphenylamine and 4-nitrosodiphenylamine was controlled as 180 kg/h, and the flow rate of methanol was controlled as 48 kg/h. The powdery composite catalyst

above-prepared was added simultaneously to the reactor so that the solid-liquid ratio by weight was 6:100. Hydrogenation-reduced liquid overflowed from the first-stage reactor into a second-stage reactor, then into a third-stage reactor, finally into a settler. The reaction temperature was 75-80° C., pressure was 1.3 MPa and total residence time was 5 h. The powdery composite catalyst was recovered as much as possible under the action of a magnetic separator. Solid-liquid mixture containing higher concentration of solid catalyst at the bottom of the settler was returned to the first-stage hydrogenation reactor via a Venturi type solid-liquid conveying device using the power of feeding stocks. The activity of the catalyst in the hydrogenation reaction was judged by monitoring the endpoint of reducing reaction, and thus it could be determined whether powdery composite catalyst for hydrogenation reaction was replenished.

[0100] The hydrogenation liquid was measured by high performance liquid chromatograph (HPLC) and was found not containing 4-nitrodiphenylamine and 4-nitrosodiphenylamine.

[0101] D. Separation II

[0102] The above hydrogenation liquid was conveyed to separation II process stage. The hydrogenation liquid was subjected to filtration to recover a minor amount of the powdery composite catalyst entrained in the hydrogenation liquid. The powdery composite catalyst recovered by filtration was recycled back to the hydrogenation process after regeneration.

[0103] The filtrate was fed at a flow rate of 228 kg/h to a methanol column, where methanol was obtained from column top and could be reused in the hydrogenation process. The bottoms was fed to an aniline column, where aniline was obtained from the column top and recycled back to the condensation process stage, and crude 4-aminodiphenylamine was obtained from column bottom. The aniline column was operated at a pressure of 0.005 MPa (absolute pressure), a column bottom temperature of 150 to 160° C., and a gas phase temperature of 115 to 125° C.

[0104] E. Refining

[0105] The crude 4-aminodiphenylamine from multiple sets of separation II equipment enters one set of refining equipment. The crude product of 4-aminodiphenylamine (containing 78.1 percent of 4-aminodiphenylamine, 21.75 percent of aniline, 0.05 percent of azobenzene and 0.1 percent of phenazine) was continuously fed to rectification column 1 at a flow rate of 120 kg/h via a gear pump. The temperature of still was controlled as 270° C., the temperature of column top was controlled as 110° C., vacuum degree was controlled as 0.094 MPa and reflux ratio was controlled as 5:1. Light components, i.e. aniline, azobenzene and phenazine, were taken out from the column top at a flow rate of about 26.2 kg/h, and conveyed to rectification column 3.

[0106] The rectification column 3 was operated at conditions of still temperature of 150° C., column top temperature of 90° C., vacuum degree of 0.094 MPa and reflux ratio of 1:1. Aniline was distilled off from column top at a flow rate of 24 kg/h, and azobenzene and phenazine were left in column bottom.

[0107] Bottoms of the rectification column 1 were conveyed to rectification column 2. The rectification column 2 was operated at conditions of still temperature of 280° C., column top temperature of 170° C., vacuum degree of 0.097 MPa and reflux ratio of 1:1. The finished 4-aminodiphenylamine was obtained at the column top of the rectification column 2.

[0108] Bottoms of the rectification column 2 were conveyed to batch still. The batch still was operated at conditions of kettle temperature of 285-320° C., vacuum degree of 0.094 MPa and top temperature of 235-250° C., to distill off the residual 4-aminodiphenylamine, which was recycled back to the rectification column 2 to be further distilled. The whole refining process of 4-aminodiphenylamine was continuously carried out. The finished 4-aminodiphenylamine product obtained had a purity of 99.1%, a melting point of 72° C. and a solidifying point of 72.4° C. The yield of the process in industrial scale production was 95.1%.

Example 4

[0109] 4-Aminodiphenylamine was prepared according to the same procedure as described in Example 3 except that condensation was carried out as follows:

[0110] Under vacuum condition, feeding pumps for the complex base catalyst, aniline and nitrobenzene were simultaneously switched on and adjusted to such flow rate as aniline 150 kg/h, nitrobenzene 30 kg/h and the complex base catalyst 200 kg/h. The aniline, nitrobenzene and complex base catalyst were continuously fed into a falling film reactor to be heated and allowed to condense. Condensation liquid in the falling film reactor was discharged from the bottom into a first reactor to proceed with condensing. Part of condensation liquid from the bottom of the first reactor was conveyed back to the falling film reactor via a circulating pump, forming a local circulating system. Ethanol vapor at 78-90° C. was used as the heat medium of the falling film reactor. Reaction temperature was controlled as 75° C., pressure was controlled as 0.008 MPa (absolute pressure) and flow rate of the circulating liquid was controlled as 1 m^3/h. The reactants overflowed from the first reactor into a second reactor. The process conditions of the second reactor, such as operational temperature and pressure, were identical with that of the first reactor. The total residence time of the reactants in the falling film reactor, first reactor and second reactor was controlled as 5 h. Once the condensation reaction became stable; the complex base catalyst recovered was used, with sodium hydroxide and tetraalkyl ammonium salt (i.e. tetramethylammnium carbonate according to Example 1) in a molar ratio of 1:1 being replenished, and the molar ratio of hydroxide ion to nitrobenzene in the reaction mixture was controlled not less than 1:1. The effluent of the second reactor was found to contain not larger than 0.1 wt.-% of nitrobenzene, 15.6 wt.-% of water and 17.6 wt.-% of 4-nitrosodiphenylamine and 4-nitrodiphenylamine.

Example 5

[0111] Process for Regenerating Catalyst

[0112] 20 g of powdery composite catalyst, which was recovered by filtration of the hydrogenation liquid, was charged into a 100 ml three-necked flask equipped with a stirrer and a thermometer. 20 ml of 40% aqueous solution of sodium hydroxide was added thereto. While stirring, the mixture was heated to 90° C. and maintained at that tem-

perature for 1 h. At the end of the reaction, the catalyst was subjected to ultrasonic washing for 30 min in a washing tank, followed by washing with water for multiple times until the pH of the washing water was 7-8. The gained solid was regenerated powdery composite catalyst.

Example 6

[0113] Preparation of a Complex Base Catalyst

[0114] To a 500 ml three-necked flask equipped with a condenser and a stirrer were added 230 g of water, followed by adding 91 g of pentahydrated tetramethyl ammonium hydroxide (containing 0.5 mol of tetramethyl ammonium hydroxide), 20 g (0.5 mol) of sodium hydroxide and 70 g of trimethyl hydroxyethyl ammonium chloride (0.5 mol). The mixture was homogeneously stirred at 75±2° C. to give a complex base catalyst having a concentration of 32.85 wt.-%.

Example 7

[0115] Preparation of a Complex Base Catalyst

[0116] To a 500 ml three-necked flask equipped with a condenser and a stirrer were added 230 g of water, followed by adding 91 g of pentahydrated tetramethyl ammonium hydroxide (containing 0.5 mol of tetramethyl ammonium hydroxide), 20 g (0.5 mol) of sodium hydroxide and 74.5 g of tetramethyl ammonium methylcarbonate ($[(CH_3)_4N]^+[CO_3CH_3]^-$)(0.5 mol). The mixture was homogeneously stirred at 75±2° C. to give a complex base catalyst having a concentration of 33.7 wt.-%.

Example 8

[0117] To a 500 ml four-necked flask equipped with a stirrer, a water segregator and a condenser were added 150 g of water, followed by adding 91 g of pentahydrated tetramethyl ammonium hydroxide (containing 0.5 mol of tetramethyl ammonium hydroxide), 20 g (0.5 mol) of sodium hydroxide and 74.5 g of tetramethyl ammonium methylcarbonate ($[(CH_3)_4N]^+[CO_3CH_3]^-$)(0.5 mol). Then 25 g of benzene were added thereto, and the mixture was heated to reflux. There were water layer and oil layer in the water segregator. Oil layer was returned to the four-necked flask and water layer was separated out until there was no water in distilled liquid. An anhydrous form of complex base catalyst was obtained.

Example 9

[0118] Preparation of Tetramethylammonium Methyl-carbonate ($[(CH_3)_4N]^+[CO_3CH_3]^-$)

[0119] To a 1.5 L autoclave equipped with a stirrer and a heating means were added 90 g (1.0 mol) of dimethyl carbonate, 59 g (1.0 mol) of trimethyl amine and 510 g (15 mol) of methanol. Stirring was initiated after the autoclave was sealed. The autoclave was heat to 140° C., and pressure was 1.5 MPa. The reaction was kept at 140° C. for 4 h. Then the reaction mixture was cooled to 50° C. and discharged into a 1L three-necked flask. Part of methanol was removed from the solution of tetramethylammonium methyl-carbonate in methanol thus obtained under vacuum, and then the solution was cooled to ambient temperature. White crystal precipitated out. The crystal was filtrated, oven dried and recrystallized from methanol, to give 119.5 g of tetramethylammonium methyl-carbonate having a purity of 99.2% as measured by chromatography. The yield was 80.2%.

Example 10

[0120] 92.5 g (1 mol) of 1-chloro-2,3-epoxy propane, 3 g (1 mol) of N-methyl diethanolamine, 2 g of sodium hydroxide and 700 g of water were charged into an autoclave with a stirrer, a heating means and a thermometric means. With stirring, the mixture was gradually heated to 120° C., then gaseous ethylene oxide was continuously passed into the autoclave to maintain a reactor pressure of 0.3 MPa until the quantity of ethylene oxide passed into reached 150 g. The reaction continued for further 2 h at that temperature, to give $ClCH_2[CH_2CH_2O]_{2-5}$—H. 60 g of gaseous trimethylamine were passed thereto. The autoclave was heat to 140° C., and pressure was 1.5 MPa. The reaction was maintained at that temperature for 4 h. Then the mixture was cooled to room temperature. After conventionally dehydrating and drying, 105 g of N,N,N-trimethyl-N-ethoxylated (1-4 moles of ethylene oxide) propyl ammonium chloride was obtained.

Example 11

[0121] Preparation of Tetramethyl Ammonium Hydroxide

[0122] To a 1.5 L autoclave equipped with a stirrer and a heating means were added 90 g (1.0 mol) of dimethyl carbonate, 59 g (1.0 mol) of trimethyl amine and 510 g (15 mol) of methanol. Stirring was initiated after the autoclave was sealed. The autoclave was heated to 140° C., and pressure was 1.5 MPa. The reaction was kept at 140° C. for 4 h. Then the reaction mixture was cooled to room temperature and discharged into a 1L three-necked flask. A slurry consisting of 148 g (2.0 mol) of calcium hydroxide and 350 g of water was added thereto. Methanol was distilled off by heating over 8 h while stirring. 355 g of tetramethyl ammonium hydroxide solution was obtained after filtration. The content of tetramethyl ammonium hydroxide was found as 24.4% and the total reaction yield was 95.2%.

Example 12

[0123] Preparation of Tetraethyl Ammonium Hydroxide

[0124] To a 1.5 L autoclave equipped with a stirrer and a heating means were added 154 g (1.0 mol) of diethyl sulfate, 101 g (1.0 mol) of triethyl amine and 690 g (15 mol) of ethanol. Stirring was initiated after the autoclave was sealed. The autoclave was heat to 140° C., and pressure was 1.0 MPa. The reaction was kept at 140° C. for 4 h. Then the reaction mixture was cooled to room temperature and discharged into a 1L three-necked flask. 80 g (2.0 mol) of sodium hydroxide was added thereto. The reaction mixture was heated at 45° C. for 4 h while stirring. After filtration, part of ethanol was distilled off from the filtrate. Then 500 g of water was added while ethanol was distilled off (part of water was entrained out), to give 604 g of tetraethyl ammonium hydroxide solution. The content of tetraethyl ammonium hydroxide was found as 23.3 wt.-% and the total reaction yield was 95.7%.

Example 13

[0125] Effect on Reaction Imposed by the Quantity of Aniline and Nitrobenzene

[0126] A local circulating system having a total volume of 1L equipped with a vacuum system and a temperature control system was comprised of a miniature reactor, a film reactor and a circulating pump. The system was firstly filled with aniline, and the flow of the circulating pump was set at 2 l/h. A mixture, containing nitrobenzene, aniline and the complex base catalyst prepared according to example 1 at a molar ratio of nitrobenzene to aniline to OH^- in the complex base catalyst of 1:1:1.8, was fed to the reactor at a flow rate of 200 ml/h. The residence time was 5 h. The system temperature was maintained at 75° C. and the system pressure was maintained at 0.008 MPa (absolute pressure). After the aniline was replaced by reaction liquid and reaction liquid was stable in composition, a sample was taken and analyzed. Nitrobenzene was substantially not detectable. The reaction selectivity was calculated according to the total mole number of 4-nitrosodiphenylamine and 4-nitrodiphenylamine generated.

[0127] The results obtained under the same conditions except that the ratio of nitrobenzene to aniline was changed were showed in table 1.

TABLE 1

Effect on reaction imposed by the quantity of aniline and nitrobenzene

No.	Nitrobenzene:aniline (mol/mol)	Reaction selectivity (%)
1	1:1	90.2
2	1:3	96.1
3	1:5	99.1
4	1:10	99.3

[0128] It can be seen from the data showed in table 1 that increasing the molar ratio of aniline to nitrobenzene will enhance the reaction selectivity, increase target products and reduce the by-products. However, in the practice, if the quantity of aniline is too large, the loss of aniline and the energy consumption during separation will increase.

Example 14

[0129] Effect on Condensation Reaction Imposed by Water

[0130] A local circulating system having a total volume of 1L equipped with a vacuum system and a temperature control system was comprised of a miniature reactor, a film reactor and a circulating pump. The system was firstly filled with aniline, and the flow of the circulating pump was set at 2 l/h. A mixing liquid containing nitrobenzene, aniline and the complex base catalyst at a molar ratio of nitrobenzene to aniline to OH^- in the complex base catalyst of 1:7:1.15 was fed to the reactor at a certain flow. The system temperature was maintained at 75° C. and the system pressure was maintained at 0.008 MPa (absolute). After the aniline was replaced by reaction liquid and reaction liquid was stable in composition, the feeding flow rate of the reaction mixture was varied to adjust the residence time. The water contents of reaction effluent, measured when the measured content of nitrobenzene was equal to or less than 0.1% and calculated yield based on 4-nitrosodiphenylamine and 4-nitrodiphenylamine generated was 97%, were listed below.

No.	Molar ratio of three components in complex base catalyst Tetramethyl ammonium hydroxide:N,N-dimethyl-N,N-bis(ethoxylated (1–4 moles of ethylene oxide) propyl) ammonium carbonate:sodium hydroxide	Water content in product (%)
1	5:2:2	5.1
2	3:2:2	10.2
3	2:2:2	15.4
4	1:2:1	17.5
5	0.5:2:0.5	19.8
6	Tetramethyl ammonium hydroxide is used as catalyst	1.2

[0131] It can be seen that water content at the end of the reaction increases as the proportion of N,N-dimethyl-N,N-bis(ethoxylated (1-4 moles of ethylene oxide) propyl) ammonium carbonate in the complex catalyst increases. Namely, with the use of a complex base catalyst according to the present invention, the range of permitted water content in the reaction mixture at the end of reaction is greatly enlarged, that is, the yield is good enough even when there is a higher content of water in the reaction system. The less the water content is in the later phase of the reaction, the lower the dehydration efficiency is, thus reaction difficulty is reduced in the process according to the present invention. If only the tetramethyl ammonium hydroxide is used as catalyst, the yield cannot reach 97% until the water content of reaction mixture is reduced to 1.2% by dehydration, which imposes difficulty to the reaction control and increases the power consumption.

Example 15

[0132] Anhydrous complex catalyst prepared in example 8 and 651 g of aniline were charged into a four-necked flask with stirring device and thermometer. With stirring, the temperature was elevated to 75° C. and pressure was reduced to 0.008 MPa (absolute pressure). Aniline was returned to the four-necked flask after demixing the water-aniline azeotrope distilled until the water content in the system is less than 0.5%. 123 g of nitrobenzene was dropwise added over 2 h, then the dehydrating was continued for 4 h. It was found via chromatographic analysis that the yield of 4-nitrosodiphenylamine and 4-nitrodiphenylamine was 97.4% and the water content in the system was less than 0.5%.

Example 16

[0133] The Comparison of Continuous Film Reaction and Complete Mixing Reaction

[0134] Continuous film reactions and complete mixing reactions were conducted under the following conditions: molar ratio of aniline to nitrobenzene to OH^- in complex base catalyst was controlled at 7.5:1:1.5, reaction temperature was 75° C., reaction time was 5 h, and reaction pressure was 0.005 MPa (absolute pressure). Results were listed in Table 2 and Table 3.

TABLE 2

Results of complete mixing reactions

No.	Conversion rate of nitrobenzene %	Yield %
1	98.1	94.6
2	98.3	95.1
3	98.1	94.8

[0135]

TABLE 3

Results of continuous film reactions

No.	Conversion rate of nitrobenzene %	Yield %
1	99.2	97.6
2	99.9	98.1
3	99.5	97.8

Example 17

[0136] Catalytic Hydrogenation in a Fixed Bed Reactor

[0137] A 400 ml of reactor was filled with copper catalyst in cylindrical shape having a diameter of 5 mm and a height of 5 mm. The catalyst contained 42% of copper oxide, 42% of zinc oxide, 6% of aluminum oxide and balance amount of physical water. Under a flow of hydrogen gas, the catalyst bed was activated at 110-240° C. for 24 hours. The organic phase containing 4-nitrosodiphenylamine and 4-nitrodiphenylamine obtained in separation I in Example 3 was molten by slightly heating and then mixed with methanol having a volume equal to 30% of the volume of the organic phase. The mixture, at a flow rate of 100 ml/h, was mixed with hydrogen gas and then preheated prior to being added to above hydrogenation reactor. The hydrogenation was performed at 135° C. under a pressure of 5.0 MPa with gas-liquid ratio being 1000:1. The hydrogenation-reduced liquid was measured by high performance liquid chromatograph (HPLC) and was found not containing 4-nitrodiphenylamine and 4-nitrosodiphenylamine. The unit was continuously operated under above conditions for 500 hours.

Example 18

[0138] Batch Hydrogenating Example

[0139] 500 g of separation I liquid containing 17.5 weight percent of 4-nitrosodiphenylamine and 3.0 weight percent of 4-nitrodiphenylamine was charged into a 1L autoclave with stirring device and temperature control device. 150 g of ethanol and 5 g of the powdery composite catalyst prepared in example 2 were added thereto. The system atmosphere was replaced with hydrogen gas for three times, and then the system was pressurized to 0.8 MPa. While stirring, the reaction mixture was heated to 100° C. and maintained at this temperature for 4 h. At the end of the reaction, the mixture was cooled, and then discharged after pressure release. The reaction liquid was analyzed via HPLC, and was found containing no 4-nitrosodiphenylamine and 4-nitrodiphenylamine but 14.6% of 4-aminodiphylamine (chromatograph content).

[0140] Comparison of Powdery Composite Catalyst and Noble Metal Catalyst

[0141] Pd/C catalyst with 5 wt. % of palladium was compared with the powdery composite catalyst according to the present invention. Experiments were carried out under the same conditions as described in above batch hydrogenating example. The quantities of catalysts used were identical, and both Pd/C catalyst and powdery composite catalyst were recovered and reused after the reaction. Within 21 times of reuse, 4-nitrosodiphenylamine was undetectable in both reaction liquids. However, at the twenty-first time of reuse, the reaction liquid obtained by using Pd/C catalyst was found containing 0.1 wt. % of 4-nitrodiphylamine while the reaction liquid obtained by using the powdery composite catalyst according to the present invention was found containing no 4-nitrodiphylamine. The results showed that the antitoxic performance of the powdery composite catalyst according to the present invention was better than that of the noble metal catalyst.

1-26. (canceled).

27. A process for preparing 4-aminodiphenylamine comprising the steps of

i) reacting nitrobenzene and aniline in presence of a complex base catalyst in a condensation reaction to form a reaction mixture comprising 4-nitrodiphenylamine and 4-nitrosodiphenylamine, said complex base catalyst comprising a tetraalkyl ammonium hydroxide, an alkali metal hydroxide, and a tetraalkyl ammonium salt;

ii) separating, recovering, and reusing the complex base catalyst;

iii) hydrogenating the reaction mixture in presence of hydrogen, hydrogenation catalyst, and a hydrogenation solvent to obtain a hydrogenation reaction product;

iv) separating, recovering, and reusing aniline and optionally the hydrogenation solvent from the hydrogenation reaction product;

v) isolating 4-aminodiphenylamine from the hydrogenation reaction product.

28. The process according to claim 27, wherein the condensation reaction step i) is carried out under conditions comprising a nitrobenzene to aniline molar ratio of about 1:1 to 1:15, reaction temperature of about 20 to 150° C., reaction pressure of about 0.005 to 0.1 MPa (absolute pressure), and reaction time of about 3.5 to 6 hours.

29. The process according to claim 27, wherein a molar ratio of hydroxide ion in the complex base catalyst to nitrobenzene is in a range of about 1:4 to 4:1.

30. The process according to claim 27, wherein a molar ratio of the tetraalkyl ammonium hydroxide to the alkali metal hydroxide to the tetraalkyl ammonium salt in the complex base catalyst is (0-9):(0.5-3):(0.5-3), and a sum of concentration of the tetraalkyl ammonium hydroxide, the alkali metal hydroxide, and the tetraalkyl ammonium salt ranges from 10 to 100 percent by weight.

31. The process according to claim 27, wherein the complex base catalyst is prepared by the steps of

stirring and mixing the tetraalkyl ammonium hydroxide, the alkali metal hydroxide or alkali metal oxide, and the tetraalkyl ammonium salt in water at a temperature of

from 0 to 90° C. to form a homogenous mixture of an aqueous form of the complex base catalyst,

wherein the tetraalkyl ammonium hydroxide, alkali metal hydroxide or oxide, and tetraalkyl ammonium salt are in solid form or aqueous solution.

32. The process according to claim 27, wherein the complex base catalyst is prepared by the steps of

stirring and mixing the tetraalkyl ammonium hydroxide, alkali metal hydroxide or oxide, and tetraalkyl ammonium salt in water at a temperature of from 0 to 90° C. until being homogeneous,

completely removing water from the homogeneous mixture by adding benzene to form an anhydrous complex base catalyst,

wherein the tetraalkyl ammonium hydroxide, alkali metal hydroxide or oxide, and tetraalkyl ammonium salt are in solid form or aqueous solution.

33. The process according to claim 27, wherein the tetraalkyl ammonium salt is represented by a general formula of

$$[(R1)(R2)(R3)(R4)N]^{+}{}_{n}X^{n-}$$

wherein R1, R2, R3 and R4, each of which may be identical or different, can be alkyl having from 1 to 4 carbon atoms, said alkyl being optionally substituted by a hydrophilic substituent; X^{n-} is selected from the group consisting of halide ion, sulfate radical, carbonate radical, phosphate radical, bicarbonate radical, bisulfate radical, C_1-C_2-alkyl carbonate radical, C_1-C_2-alkyl sulfate radical; and n is a value of from 1 to 2.

34. The process according to claim 33, wherein at least one of R1, R2, R3 and R4 is substituted by a hydrophilic substituent selected from the group consisting of hydroxy, methoxy, polyether, cationic polyamide, polyester, polyethylene polyamine, and highly water-soluble quaternary ammonium salt-containing radical.

35. The process according to claim 33, wherein the tetraalkyl ammonium salt is a hydrophilic substituent-carrying tetraalkyl ammonium salt selected from the group consisting of poly-methylated triethylene tetraamine sulfate, poly-methylated diethylene triamine carbonate, N,N-dimethyl-N,N-bis(methoxyethyl) ammonium carbonate, N-methyl-N,N,N-tri(methoxyethyl) ammonium carbonate, N,N,N-trimethyl-N-hydroxyethyl ammonium carbonate, trimethyl hydroxyethyl ammonium chloride, N,N,N-trimethyl-N-ethoxylated (1-4 moles of ethylene oxide) ethyl ammonium carbonate, N,N,N-trimethyl-N-ethoxylated (1-4 moles of ethylene oxide) propyl ammonium carbonate, N,N,N-trimethyl-N-ethoxylated (1-4 moles of ethylene oxide) propyl ammonium chloride, and N,N-dimethyl-N,N-bis(ethoxylated (1-4 moles of ethylene oxide) propyl) ammonium carbonate.

36. The process according to claim 33, wherein the tetraalkyl ammonium salt is selected from the group consisting of tetramethyl ammonium carbonate, tetramethyl ammonium methyl-carbonate, tetraethyl ammonium carbonate, tetraethyl ammonium ethyl-carbonate, tetramethyl ammonium sulfate, tetramethyl ammonium methyl-sulfate, tetraethyl ammonium sulfate, and tetraethyl ammonium ethyl-sulfate.

37. The process according to claim 33, wherein the tetraalkyl ammonium salt is prepared by the step of

reacting a trialkyl amine with a di(C_1-C_2)alkyl carbonate or di(C_1-C_2)alkyl sulfate in a polar solvent.

38. The process according to claim 37, which is undertaken under reaction conditions comprising a reaction pressure ranging from 0.1 to 3.0 MPa, a reaction temperature ranging from 50 to 200° C., a reaction time ranging from 1.5 to 6 hours, a molar ratio of trialkyl amine to di(C_1-C_2)alkyl carbonate or di(C_1-C_2)alkyl sulfate ranging from 2:1 to 1:2, the polar solvent is methanol, ethanol, or isopropanol, and the polar solvent is in an amount of from 1 to 10 times of weight of the trialkyl amine.

39. The process according to claim 27, wherein the condensation reaction of step i) is performed in the absence of oxygen.

40. The process according to claim 27, wherein the condensation reaction of step i) is performed in the absence of addition or control of proton materials.

41. The process according to claim 27, wherein the condensation reaction of step i) is performed in the absence of a solvent.

42. The process according to claim 27, wherein the complex base catalyst is added at an initiation of the condensation reaction and only tetraalkyl ammonium salt, or alkali metal hydroxide or oxide, or both are replenished during the course of the reaction.

43. The process according to claim 27, wherein step i) the condensation reaction is conducted in a circulating system comprising a condensing circulating pump, a falling film reactor, and a reactor.

44. The process according to claim 27, wherein a falling film reactor is used in step i), and the falling film reactor employs a heat medium selected from the group consisting of ethanol vapor, hot water, steam, and methanol vapor.

45. The process according to claim 27, wherein in step ii), the complex base catalyst is recovered by neutralizing the reaction mixture with an acidic material to form an aqueous phase, and basifying the aqueous phase using a base,

wherein said acidic matter is selected from the group consisting of an inorganic acid, a combination of an oxide of the inorganic acid and water, and an inorganic acid salt, and

wherein said base is selected from the group consisting of a hydroxide or oxide of alkali metal and alkaline earth metal.

46. The process according to claim 45, wherein the acidic material are chosen according to the tetraalkyl ammonium salt of the complex base catalyst and the base are chosen according to the base of the complex base catalyst.

47. The process according to claim 45, wherein the acidic material is selected from the group consisting of hydrochloric acid, sulfuric acid, nitric acid, carbonic acid, sodium bicarbonate, a combination of carbon dioxide and water, and a combination of sulfur trioxide and water.

48. The process according to claim 27, wherein the hydrogenation catalyst comprises an active component selected from the group consisting of a Group VIII element, Cu, Cr, Zn and Mn, and optionally a co-catalyst component.

49. The process according to claim 27, wherein the hydrogenation catalyst is a powdery composite catalyst comprising nickel, aluminum, and a component A, said component A is at least one selected from the group consisting of Fe, Cu, Co, Mn, Cr, Mo, B, and P.

50. The process according to claim 49, wherein nickel is at a range from about 25 to 99.9 wt %, and a total of aluminum and the component A is at a range from about 0.1 to 75 wt %.

51. The process according to claim 27, wherein the step iii) hydrogenation reaction is carried out with hydrogen as reducing agent; a volume ratio of gas to liquid is in a range of from about 10:1 to 1500:1; a weight ratio of solid to liquid is in a range of from about 0.5:100 to 16:100 when a non-fixed bed hydrogenation process is used; and a weight ratio of solvent to step ii) condensation liquid from which the complex base catalyst has been separated in a range of from about 1:10 to 5:10;

wherein the liquid includes solvent and step ii) condensation liquid from which the complex base catalyst has been separated, and the solid represents the hydrogenation catalyst;

wherein step iii) hydrogenation reaction is carried out at a temperature of about 50 to 150° C., a pressure of about 0.2 to 6.0 MPa (absolute pressure), and a reaction time ranges from 2 to 7 hours.

52. The process according to claim 50, wherein the powdery composite catalyst is prepared by

mixing powdery nickel, powdery aluminum, and the component A in the weight range to obtain a mixture,

melting the mixture,

pulverizing the melt mixture into powder after discharging and quenching, and

treating the pulverized powder with an aqueous solution of a hydroxide.

53. The process according to claim 27, wherein a solvent for the hydrogenation reaction of step iii) is selected from the group consisting of an alcohol, water, and a mixture thereof.

54. The process according to claim 27, further comprising

separating, recovering, and reusing the hydrogenation catalyst after the hydrogenation step iii),

wherein the hydrogenation catalyst is optionally at least partially regenerated prior to being reused.

55. The process according to claim 49, wherein a magnetic separator is used to recover magnetic powdery composite catalyst at step iv).

56. The process according to claim 55, wherein the powdery composite catalyst is spent and regenerated by treating with ultrasonic vibration, or strong base, or both.

57. The process according to claim 27, wherein the recovered powdery composite catalyst is conveyed back to the hydrogenation step reactor via a Venturi tube.

58. The process according to claim 27, wherein the step v) refining is performed in a three-column continuous process and a batch rectification process,

wherein column 1, 2, and 3 are operated at a pressure ranging independently from about 0.09 to 0.098 MPa; a still temperature of from about 260 to 290° C., from about 260 to 300° C., and from about 120 to 170° C., respectively; a reflux ratio of from about 2:1 to 10:1, from about 1:0.5 to 1:4, and from about 1:0.5 to 1:2, respectively; and the batch rectification column is operated at a pressure of from about 0.09 to 0.098 MPa, and a still temperature of from about 280 to 330° C.

59. A process for preparing 4-aminodiphenylamine comprising the steps of:

(i) continuously feeding nitrobenzene, aniline, and a complex base catalyst to condensation reactor via metering pumps, and allowing them to react to form a condensation liquid containing 4-nitrodiphenylamine, 4-nitrosodiphenylamine, and salts thereof;

(ii) continuously feeding the condensation liquid to a separation I reactor, where the complex base catalyst is recovered by neutralizing the condensation liquid with an acidic material to conduct separation and obtain an aqueous phase, basifying the aqueous phase by a base, and recycling the recovered complex base catalyst to the condensation reactor;

(iii) continuously feeding liquid from the separation I reactor and a hydrogenation solvent to a hydrogenation reactor, and allowing to react with hydrogen gas in the presence of a powdery composite catalyst to form a hydrogenation liquid containing 4-aminodiphenylamine;

(iv) feeding the liquid from step iii) to a separation II reactor, where the powdery composite catalyst, which is to be recycled to the hydrogenation reactor directly or after being at least partially regenerated, aniline, which is to be recycled to the condensation reactor, and optionally, hydrogenation solvent, which is to be recycled to the hydrogenation reactor, are obtained;

(v) feeding crude 4-aminodiphenylamine, from which most of aniline has been separated in step iv), to a refining reactor, where partial aniline, which is to be recycled back to the condensation reactor, and refined 4-aminodiphenylamine are obtained, and refined 4-aminodipheylamine is obtained.

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CONFIDENTIAL BUSINESS INFORMATION SUBJECT TO PROTECTIVE ORDER

UNITED STATES INTERNATIONAL TRADE COMMISSION
WASHINGTON, D.C.

Before the Honorable Paul J. Luckern

In the Matter of CERTAIN RUBBER ANTIDEGRADANTS, COMPONENTS THEREOF, AND PRODUCTS CONTAINING SAME	Investigation No. 337-TA-533

FLEXSYS AMERICA L.P.'S POST-HEARING BRIEF

Pursuant to Ground Rule No. 18, Flexsys America L.P. hereby submits its proposed Post-Hearing Brief.

Gregory C. Dorris
Charles H. Carpenter
PEPPER HAMILTON LLP
Hamilton Square
600 Fourteenth Street, N.W.
Washington, DC 20005
((202) 220-1200

Glen Belvis
Brinks Hofer Gilson & Lione
455 North Cityfront Plaza Drive
Suite 3600
Chicago, Illinois 60611
(312) 321-4200

Eric C. Cohen
Neil A. Benchell
Carolyn E. Miller
KATTEN MUCHIN ROSENMAN LLP
525 West Monroe Street
Chicago, Illinois 60661-3693
(312) 902-5200

Attorneys for Complainant Flexsys America L.P.

controlled amount of protic material to produce one or more 4-ADPA intermediates." (CFF 287 – 289, 310 – 312.)

Respondents' expert, Dr. Fu, conceded that if Flexsys' proposed claim construction of "controlled amount of protic material" is adopted, then Sinorgchem's process literally meets that element of the claims of the patents-in-suit. (CFF 418.) Respondents raise no other non-infringement argument. Thus, the issue of literal infringement hinges on the proper interpretation of "controlled amount of protic material."

In plain English, the reaction occurs "in the presence of . . . a controlled amount of protic material." (CFF 288 – 289, 311 – 312.) The patent teaches that protic material must be controlled between a maximum and a minimum in order to obtain high conversion of nitrobenzene and to maintain selectivity of the desired 4-ADPA intermediates. (CFF 333, 334.) The patent also teaches that the maximum and minimum depend on the reaction conditions, including as the type and amount of base, and other conditions (CFF 332, 346.)

The proper construction of "controlled amount of protic material" is an amount up to that which inhibits the reaction of aniline and nitrobenzene and a minimum amount necessary to maintain selectivity. (See Section V. B., infra.) This construction is consistent with all of the teachings of the patent. It is consistent with Example 10, in which an excess of aniline is used as the solvent, and which provides the best results of all of the examples in the '063 patent: 100 percent of the nitrobenzene is converted into product, and of that, 92.8 percent are 4-ADPA intermediates. (CFF 263 – 269.) As both

Example 8 of the '063 and '111 Patents					
Volume (μL) Water Added	% Water	% Conversion Nitrobenzene	Yield (mmole) 4-NDPA + p-NDPA	% Yield of 4-NDPA + p-NDPA	% Selectivity of 4-NDPA + p-NDPA
0	2.3	89	1.5	78.9	88.7
50	3.5	73	0.99	52.1	71.4
150	6	63	0.62	32.6	51.7
300	9.75	12	0.23	12.1	101
500	14.7	3	0.05	2.6	86.7

1. Nitrobenzene is 1.9 mmole, aniline is 2.1 mmole, and tetramethylammonium hydroxide dihydrate is 2.5 mmole
2. % Conversion = (molar amount of nitrobenzene consumed) / (molar amount of added nitrobenzene)
3. % Yield of 4-NDPA and p-NDPA = (molar amount of 4-NDPA and p-NDPA produced) / (molar amount of added nitrobenzene)
4. % Selectivity of 4-NDPA and p-NDPA = (molar amount of 4-NDPA and p-NDPA produced) / (molar amount of nitrobenzene consumed)
5. % Selectivity of 4-NDPA and p-NDPA = (% Yield of 4-NDPA and p-NDPA) / (% Conversion)

PUBLIC VERSION

> CONFIDENTIAL BUSINESS INFORMATION SUBJECT TO PROTECTIVE ORDER <

UNITED STATES INTERNATIONAL TRADE COMMISSION
WASHINGTON, D.C.

Before the Honorable Paul J. Luckern

In the Matter of CERTAIN RUBBER ANTIDEGRADANTS, COMPONENTS THEREOF, AND PRODUCTS CONTAINING SAME	Investigation No. 337-TA-533

POST-HEARING BRIEF OF RESPONDENTS SINORGCHEM CO., SHANDONG, KOREA KUMHO PETROCHEMICAL CO., LTD. AND SOVEREIGN CHEMICAL COMPANY

In sum, the express definition of "controlled amount of protic material" in the patents provides for an about 4% upper limit on water, when aniline is the solvent.

V. NON-INFRINGEMENT

A. Legal Standards

1. The Burden of Proof Is on the Complainant

In a Section 337 investigation of alleged infringement of a patent process, as here, the complainant has the burden of proof that the imported goods have been made by the patented process. In order to carry its burden, Flexsys must establish the alleged infringement by a preponderance of the evidence. *Ultra-Tex Surfaces, Inc. v. Hill Bros. Chem. Co.*, 204 F.3d 1360, 1364 (Fed. Cir. 2000); *Rohm and Haas Co. v. Brotech Corp.*, 127 F.3d 1089, 1092 (Fed. Cir. 1997).

2. Infringement Can Be Direct or Indirect

An entity may be shown to infringe an asserted claim of a patent either directly or indirectly. Direct infringement is governed by Section 271(a). 35 U.S.C. § 271(a). Indirect infringement is governed by Sections 271(b) and (c). 35 U.S.C. §§ 271(b) and (c).

In order to directly infringe a process claim, a party must perform each and every recited step of the claimed process. *RF Delaware, Inc., v. Pacific Keystone Techs., Inc.* 326 F.3d 1255, 1267 (Fed. Cir. 2005); *Canton Bio-Medical, Inc. v. Integrated Liner Techs., Inc.*, 216 F.3d 1367, 1370 (Fed. Cir. 2000); *Joy Techs., Inc. v. Flakt, Inc.*, 6 F.3d 770, 773 (Fed. Cir. 1993). This rule applies to determining direct infringement under Section 271(a) and to determining infringement under Section 271(g), which prohibits the importation, sale, or use within the United States of a product made outside the United States by a process patented in the United States. *See Avery Dennison Corp. v. UCB Films PLC*, 1997 WL 665795, at *2 (N.D. Ill. Oct. 20, 1997) (court held "like § 271(a), § 271(g) imposes liability for direct infringement," and found no direct

infringement where defendant was alleged to have performed only the initial step of the process patent).

Indirect infringement may be established by proving a party actively induced infringement by another. 35 U.S.C. § 271(b). There can be no inducing infringement without proof of direct infringement by another. *Joy Techs.*, 6 F.3d at 774-775. In order to establish inducing infringement, Flexsys must show that Sinorgchem or KKPC knowingly and intentionally caused another to directly infringe an asserted claim. *MercExchange, L.L.C. v. eBay, Inc.*, 401 F.3d 1323, 1332-33 (Fed. Cir. 2005); *Hewlett-Packard Co. v. Bausch & Lomb, Inc.*, 909 F.2d 1464, 1469 (Fed. Cir. 1990).

Indirect infringement may also be established by proving a party contributed to infringement by another. 35 U.S.C. § 271(c). Contributory infringement requires proof that a party offered to sell, sold, or imported into the United States a component of a patented apparatus, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, and knowing the component, material, or apparatus to be especially made or adapted for use in infringing the patent, the component, material, or apparatus not being a staple article of commerce having a substantial non-infringing use. 35 U.S.C. § 271(c); *Hewlett-Packard Co.*, 909 F.2d at 1469. There can be no contributory infringement without proof of direct infringement by another. *Joy Techs.*, 6 F.3d at 774-775.

3. Literal Infringement and Doctrine of Equivalents

Infringement can be found "literally" or under the so-called "doctrine of equivalents." In order to prove literal infringement, Flexsys must show that each and every element of an asserted claim is present exactly in an accused Sinorgchem or KKPC process. *Strattec Sec. Corp. v. Gen. Auto. Specialty Co., Inc.*, 126 F.3d 1411, 1418 (Fed. Cir. 1997). In order to prove infringement under the doctrine of equivalents, Flexsys must show that an accused process contains each and

every element of an asserted claim or its substantial equivalent. *Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 39-40 (1997). An element of an accused device or process can be found to be an equivalent of a recited claim element if it differs only insubstantially from the claimed element. *Id.* For example, an accused element may be found to be the substantial equivalent of a claim element if it performs substantially the same function, in substantially the same way, to produce substantially the same result as the claimed element. *Graver Tank & Mfg. Co., v. Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950); *Tanabe Seiyaku Co., Ltd. v. Int'l Trade Comm'n*, 109 F.3d 726, 732 (Fed. Cir. 1997); *Spectra Corp. v. Lutz*, 839 F.2d 1579, 1582 (Fed. Cir. 1988). Applied to process claims, it has been held that infringement under the doctrine of equivalents requires proof that the accused process "perform[s] substantially the same steps as the patented process, in substantially the same way, to obtain the same result." *Fromson v. Anitec Printing Plates, Inc.*, 132 F.3d 1437, 1446 (Fed. Cir. 1997).

4. **Infringement Analysis is a Two-Step Process**

The determination of whether an accused product or process infringes a patent, either directly or indirectly, is a two-step process. First, as a matter of law, the Court must determine "the meaning and scope of the patent claims asserted to be infringed." *Markman*, 52 F.3d at 976; *see also Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1572 (Fed. Cir. 1997).

Second, the properly construed claims are compared to the accused process. *See Markman*, 52 F.3d at 976; *Regents*, 119 F.3d at 1572. The comparison is made to determine whether every claim limitation is present in the accused process either literally or equivalently. *See generally Cole v. Kimberly-Clark Corp.*, 102 F.3d 524, 532 (Fed. Cir. 1996).

B. The Sinorgchem Process Does Not Literally Infringe Because It Lacks a "Controlled Amount of Protic Material"

For literal infringement, each limitation of a claim must be satisfied exactly. *See Strattec Sec. Corp.*, 126 F.3d at 1418; *see also Telemac Cellular Corp. v. Topp Telecom, Inc.*, 247 F.3d 1316, 1330 (Fed. Cir. 2001) ("Any deviation from the claim precludes such a finding [of literal infringement]." (internal citation omitted)); *Mas-Hamilton Group v. LaGard, Inc.*, 156 F.3d 1206, 1211 (Fed. Cir. 1998) ("To prove literal infringement, the patentee must show that the accused device contains every limitation in the asserted claims . . . . If even one limitation is missing or not met as claimed, there is no literal infringement." (internal citations omitted)).

As shown earlier, the '063 and '111 patents expressly define a "controlled amount of protic material" to mean that the water must be less than about 4%, when aniline is the solvent.

[ ] For this reason, the Sinorgchem process does not literally meet the claim limitation of "controlled amount of protic material" and, therefore, does not literally infringe the asserted claims of the '063 and '111 patents.

C. Sinorgchem's 4-ADPA and 6PPD Processes Do Not Infringe Under the Doctrine of Equivalents[11]

Flexsys is precluded from relying on the doctrine of equivalents as a matter of law because:

- it disavowed claim coverage for processes having more than about 4% water, when aniline is the solvent; and

[11] Although the ALJ allowed Flexsys to pursue this argument, Respondents maintain their objection that Flexsys has waived any argument of infringement under the doctrine of equivalents by failing to make any such contention in its discovery responses.

- Flexsys cannot use the doctrine of equivalents to "vitiate" the claim term "controlled amount of protic material."

In any event, the Sinorgchem process is, as a matter of fact, not equivalent to the Flexsys patent claims.

1. Flexsys Cannot Use the Doctrine of Equivalents to Erase Its Disavowal of Claim Scope

When a patentee clearly disavows a claim construction, application of the doctrine of equivalents is precluded. *See Astrazeneca AB,* 384 F.3d at 1339-40 ("The specification's clear disavowal of nonsurfactant solubilizers precludes the application of the doctrine of equivalents to recapture the disavowed solubilizers."); *Gaus v. Conair Corp.*, 363 F.3d 1284, 1291 (Fed. Cir. 2004) ("Having disavowed coverage of [particular] devices . . . the patentee cannot reclaim that surrendered claim coverage by invoking the doctrine of equivalents."); *SciMed,* 242 F.3d at 1345 ("A particular structure can be deemed outside the reach of the doctrine of equivalents because that structure is clearly excluded from the claims whether the exclusion is express or implied.").

Flexsys' deliberate and repeated statements defining the amount of protic material as no higher than about 4% when aniline is the solvent is a clear disavowal of a process, like Sinorgchem's,[ ] Indeed, Flexsys clearly emphasized that only water under about 4% is "acceptable," thereby disavowing water levels over about 4% as unacceptable. Sinorgchem's process, as a matter of law, is precluded from infringing the asserted claims of the '063 and '111 patents by equivalents.

2. Flexsys Cannot Use the Doctrine of Equivalents to Vitiate a Claim Limitation

The doctrine of equivalents cannot be used in a manner that would vitiate or eliminate a claim term. *Warner-Jenkinson,* 520 U.S. at 29-30. In *Warner-Jenkinson,* the Supreme Court urged a "special vigilance against allowing the concept of equivalence to eliminate" a claim

element. *Id.* at 40. *See also Freedman Seating Co. v. American Seating Co.*, 420 F.3d 1350, 1362 (Fed. Cir. 2005) ("This is the precise type of overextension of the doctrine of equivalents that the claim vitiation doctrine is intended to prevent."); *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1160 (Fed. Cir. 1998) (a claim for a device with a "generally conical outer surface" was not infringed by a device with a hemispherical shape because that would have written the limitation out of the claim.); *Phillips Petroleum Co. v. Huntsman Polymers Corp.*, 157 F.3d 866, 877 (Fed. Cir. 1998) (court refused to apply doctrine of equivalents in a way that would effectively read the "block copolymers" limitation out of the claims).

[ ]

Flexsys cannot use the doctrine of equivalents to extend the asserted claims to cover any amount of water, so long as "it works." That would effectively vitiate the claim term "controlled amount of protic material," as defined by the patentees to limit the water amount to about 4%, when aniline is the solvent, and is legally impermissible.

3. Sinorgchem's Process Is Substantially Different From the Claimed Process

Even if Flexsys were not precluded, as a matter of law, from proving equivalents, Flexsys cannot meet its burden of proving, on a factual basis, that the differences between Sinorgchem's process and the asserted claims are "insubstantial." Even if each claim limitation is not satisfied exactly, infringement can still be found under the doctrine of equivalents, but only where the difference between the claim limitation and a corresponding element in the accused process is "insubstantial." *See Warner-Jenkinson,* 520 U.S. at 39-40. Under the doctrine of equivalents, "[the patentee] ha[s] a duty to submit evidence tending to show equivalence with respect to limitations not literally met by the accused infringing device." *General Mills, Inc. v. Hunt-*

Wesson, Inc., 103 F.3d 978, 985 (Fed. Cir. 1997) (internal citation omitted). Flexsys has not met its burden on the issue of equivalents.

The only evidence Flexsys has submitted on infringement under the doctrine of equivalents is the conclusory and unsupported statements of its expert, Dr. Crich. Dr. Crich concludes, without any support, that the differences between Sinorgchem's process and the claimed process are not substantial because "Sinorgchem practices the same fundamental chemistry." (RFF 5.40.) Dr. Crich offers no data or test results to support his conclusory opinion. He admitted that he never conducted any tests relating to the Sinorgchem condensation process and that he considered it "unnecessary" to visit the Sinorgchem facility to observe the process. (RFF 5.10, 5.11.) Such conclusory, nonparticularized testimony of experts is legally-inadequate evidence to prove infringement under the doctrine of equivalents. *Network Commerce, Inc. v. Microsoft Corp.*, 422 F.3d 1353, 1363 (Fed. Cir. 2005) ("Generalized testimony as to the overall similarity between the claims and the accused infringer's product or process will not suffice.") "The expert declaration . . . supporting infringement by equivalents [that] are generalized and do not provide particularized testimony and linking argument on a limitation-by-limitation basis" will not defeat summary judgment of noninfringement under the doctrine of equivalents. *Id. See also Texas Instruments, Inc. v. Cypress Semiconductor Corp.*, 90 F.3d 1558, 1568-69 (Fed. Cir. 1996) (patentee failed to provide evidence sufficient to support a finding of equivalence.) Flexsys has not met its legal burden under the doctrine of equivalents.

In contrast to Dr. Crich's conclusory and unsupported opinion, Sinorgchem has established that there are numerous, substantial differences between the Sinorgchem process and the claimed process.

[

] The specific language in the specifications of the two patents, coupled with Examples 3 and 8, admonishes one of ordinary skill in the art *not* to use more than 4% water in the reaction when aniline is the solvent. [

] Moreover, one of ordinary skill in the art would interpret about 4% to be at most 4.49%. (RFF 4.27.) [

] *Tanabe*, 109 F.3d at 732 ("the claim language itself, and the specification, suggest that substituting butanone for acetone is not an insubstantial change").

Second, Mr. Wang described how Sinorgchem conducted numerous laboratory tests and pilot plant tests between 1998 and 2000 in order to develop its process. (RFF 3.11 – 3.14) [

] Thus, while Sinorgchem's conduct is evidence that it designed around the

[12] Sinorgchem's expert, Dr. Fu, is more credible than Dr. Crich, since Dr. Fu observed and learned about the Sinorgchem process during a visit to the Sinorgchem facility in China in August of 2005. (RFF 5.7.)

'063 and '111 patents, Sinorgchem's extensive research efforts lead to the conclusion that [ ]is not interchangeable with the teachings in the '063 and '111 patents that less than about 4% water is necessary when aniline is the solvent. *Id.* ("The extensive experimentation performed by Fermien, [the alleged infringer] which involved a variety of solvents, bases and reaction conditions, suggests that Fermien's activities are better described as designing around . . . . Moreover, these experiments support the conclusion that butanoane is not readily interchangeable with acetone in the claimed process.").

Third, another significant feature of the Sinorgchem process is[

]

Indeed, according to Sinorgchem's published U.S. Patent Application, the increased level of water in the Sinorgchem process does not decrease the selectivity of the desired products or adversely affect the conversion rate. (RFF 5.23, 5.24, RX-5.25, RX-707 at ¶ [0051].) Moreover,

[

]*Spectra Corp. v. Lutz*, 839 F.3d 1579 (Fed. Cir. 1988).

Fourth, in addition to the differences in the water content, there are additional substantial differences between the Sinorgchem process and the claimed process. [

]

[

]

Fifth, Sinorgchem also uses unique equipment in its process, further demonstrating that its process does not produce 4-ADPA in the same way as the process claimed in the '063 and '111 patents.[

] These unique features further establish that the differences between Sinorgchem's process and the claimed process are substantial.[13]

In sum, Flexsys is precluded, as a matter of law, from relying on the doctrine of equivalents because of its express disavowal of claim scope and the law prohibiting vitiation of claim limitations. Moreover, if one were to consider the factual issues underlying equivalents,

[13] Flexsys' expert, Dr. Crich, had little or no understanding of the equipment used in Sinorgchem's process, such as the falling film reactor and the ultrasonic reactor. (RFF 5.31, 5.33, 5.36.) Moreover, he declined to visit Sinorgchem's production facilities. (RFF 5.10.) Thus, Dr. Crich, could not offer and has not offered any persuasive testimony on these issues.

Flexsys has not come close to satisfying its burden of proving infringement under the doctrine of equivalents.

D. Sinorgchem Does Not Indirectly Infringe

Flexsys cannot prevail in proving that Sinorgchem indirectly infringed any of the asserted claims. To prevail on its theory of indirect infringement, Flexsys must first prove that Sinorgchem directly infringed the asserted claims. *See Dynacore Holdings Corp. v. U.S. Philips Corp.*, 363 F.3d 1263, 1274 (Fed. Cir. 2004). As shown above, the Sinorgchem process does not infringe, literally or under the doctrine of equivalents. Thus, in the absence of such direct infringement, there can be no liability for inducing infringement or contributory infringement. *Id.*

E. KKPC's Commercial 6PPD Processes Do Not Directly Infringe

KKPC produces 6PPD commercially under the trade name Kumanox-13. (RFF 3.88, 3.89, 5.46.) [

]

Flexsys contends that KKPC's process for producing Kumanox-13 directly infringes process claims 30 and 61 of the '063 patent and process claims 7 and 11 of the '111 patent. Claim 30 of the '063 patent and claim 7 of the '111 patent are both directed to a process for producing 4-ADPA. (RFF 1.38, 1.39, 2.2, 2.4.) Each of these claims recites three primary steps: (a) bringing aniline and nitrobenzene into reactive contact; (b) reacting the aniline and nitrobenzene in the presence of a suitable base, suitable solvent and controlled amount of protic material to produce 4-ADPA intermediates; and (c) hydrogenating the 4-ADPA intermediates to produce 4-ADPA. (RFF 2.2, 2.4.) Claim 61 of the '063 patent and claim 11 of the '111 are both directed to a process for producing 6PPD. (RFF 1.38, 1.40, 2.3, 2.5.) These claims recite four primary steps, the first three of which are essentially identical to the first three steps of claims 30

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UNITED STATES INTERNATIONAL TRADE COMMISSION
WASHINGTON, D.C.

Before the Honorable Paul J. Luckern

In the Matter of CERTAIN RUBBER ANTIDEGRADANTS, COMPONENTS THEREOF, AND PRODUCTS CONTAINING SAME	Investigation No. 337-TA-533

POST-HEARING REPLY BRIEF OF RESPONDENTS SINORGCHEM CO., SHANDONG, KOREA KUMHO PETROCHEMICAL CO., LTD. AND SOVEREIGN CHEMICAL COMPANY

Sinorgchem's process literally meets that element of the asserted claims of the patent-in-suit." (Flex. Br. at 3, CFF 418.) Quite the contrary, Dr. Fu clearly said Sinorgchem's process would not infringe the asserted claims, *even under* Flexsys' proposed claim construction, because one of ordinary skill in the art would still go to the express definition of controlled amount of protic material in column 4 of the specification of the '063 patent and conclude that, when aniline is the solvent, the "maximum" amount of water must be about 4%:

> So I would say that even with Dr. Crich's [Flexsys'] claim construction, as I said, the test of the specification doesn't change, there is explicit discussion in four different places in column 4 about 4 percent water, and, again it specifically addresses the issue in which aniline is a solvent and TMAH is the base.

(Fu, Tr. 1468:6-12, RFF 4.46.) Therefore, even under Flexsys' overbroad claim construction requiring a "maximum," the patentees' express definition of "controlled amount of protic material," when aniline is the solvent in column 4 of the '063 patent, would lead to the conclusion that Sinorgchem's process, which always has significantly more than about 4 percent water, does not infringe the asserted claims.

B. Flexsys Has Failed To Prove Infringement Under The Doctrine Of Equivalents

As described in detail in Respondents' Post-Hearing Brief, Sinorgchem's process does not infringe under the doctrine of equivalents for two legal reasons. (Resp. Br. at 44-51.) First, Flexsys cannot use the doctrine of equivalents to erase its disavowal of claim scope. (*See* Resp. Br. at 44-46.) Second, Flexsys cannot use the doctrine of equivalents to vitiate the "controlled amount of protic material" claim limitation. (*See* Resp. Br. at 45-46.) Flexsys has not addressed either of these legal arguments.

The factual issues regarding the doctrine of equivalents relate to whether the accused Sinorgchem process has an equivalent feature to the claimed limitation of "controlled amount of

protic material." Flexsys has chosen to ignore the clear definition of controlled amount of protic material when aniline is the solvent that the patentees set forth in the '063 patent and reaffirmed in the '111 patent. Instead, rather than focusing on this claim limitation, Flexsys recites a litany of other unrelated reaction variables and then concludes, again without explanation, that Sinorgchem's process is equivalent to the process set forth in the asserted claims. (Flex. Br. at 63-67.) Moreover, Flexsys improperly bases its equivalence argument on a comparison of Sinorgchem's process and examples in the patents. (Flex. Br. at 63-67.) *See Johnson & Johnston Assoc. Inc. v. R.E. Service Co., Inc.*, 285 F.3d 1046, 1052 (Fed. Cir. 2002) (*en banc*) ("Infringement, either literally or under the doctrine of equivalents, does not arise by comparing the accused product with a preferred embodiment described in the specification.").

The reaction conditions relied upon by Flexsys (e.g., temperature, pressure, yield, selectivity, base) do not relate to the claim limitation at issue: a controlled amount of protic material. For example, the fact that Sinorgchem "varied the temperature" does not relate to the question of whether Sinorgchem uses a controlled amount of protic material in its process.[8] It is a fundamental principle of patent law that the patentee asserting infringement under the doctrine of equivalents has "a duty to submit evidence tending to show equivalence with respect to limitations not literally met by the accused infringing device." *General Mills, Inc. v. Hunt-Wesson, Inc.*, 103 F.3d 978, 985 (Fed. Cir. 1997); *see also Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 39-40 (1997). Flexsys has not presented such evidence and, thus, has not met its burden of showing infringement under the doctrine of equivalents.

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[8] Moreover, Flexsys' insistence that its claimed process can cover any pressure, temperature, yield, base or amount of protic material, without providing any quantifiable guidelines, accentuates the indefiniteness of the claims under Flexsys' claim construction.

The only basis for Flexsys' argument on equivalents is Dr. Crich's conclusory opinion that, since "Sinorgchem's process practices the same basic chemistry as taught in the patents," it must be equivalent. (Flex. Br. at 63; CFF 432.) This opinion is devoid of factual support and linking arguments on a limitation by limitation basis and is, thus, insufficient to establish infringement as a matter of law. *Network Commerce, Inc. v. Microsoft Corp.*, 422 F.3d 1353, 1363 (Fed. Cir. 2005). Moreover, that opinion is factually flawed. Flexsys never identifies the basic chemistry. If that "basic chemistry" is reacting aniline and nitrobenzene in the presence of base to produce a 4-ADPA intermediate, that "basic chemistry" was taught by Wohl in 1903 and again described in 1947 by Welcher. (RX-857.) Welcher, citing Wohl, specifically teaches reacting aniline and nitrobenzene in the presence of base to produce a 4-ADPA intermediate, 4-NODPA. (RX-857 at SCS014063.) Therefore, there can be no infringement under the doctrine of equivalents simply based on Sinorgchem reacting aniline and nitrobenzene in the presence of a base.

The clear fact is that[

] Flexsys does not dispute, indeed it has no basis to dispute, the fact[

] This feature alone demonstrates that there is no equivalence.[ ]

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[9] Flexsys mischaracterizes Dr. Fu's testimony when it asserts that Dr. Fu agreed that the reactions could be run at more than 4% water when aniline is the solvent. (Flex. Br. at 63-64.) Dr. Fu testified that it would not be "impossible" to run the reaction using more than 4% water, but that is not the point. The point is that the patentees unequivocally defined "controlled amount of protic material" as about 4% water when aniline is the solvent. That definition is controlling, not what might be theoretically possible.

[

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In sum, the Sinorgchem process does not have a controlled amount of protic material or its equivalent.

C. The Commission Should Rule On The Issue Of Whether KKPC's P1/P2 Processes Infringe The Patents-In-Suit

ITC precedent and policy dictate that the Commission should rule on the issue of whether KKPC's P1 and P2 processes infringe the patents-in-suit. As requested by the ALJ, this issue has been fully briefed in KKPC's Opposition to Complainant's Motion to Strike Testimony and Exhibits Regarding Whether KKPC's P1 and P2 Processes Infringe U.S. Patent Nos. 5,117,063 and 5,608,111, filed concurrently with this Rebuttal Post-Hearing Brief. KKPC's arguments as set forth in its Opposition are incorporated by reference as if fully set forth herein.

IV. FLEXSYS CANNOT ESTABLISH THE TECHNICAL PRONG OF DOMESTIC INDUSTRY

Flexsys cannot show that its process practices any of the asserted claims of the '063 and '111 patents. Each asserted claim includes the limitation of a "controlled amount of protic material." (CFF 288-289, 311-312; SFF 50; RFF 4.4.) There is no dispute that the Flexsys process – as implemented in the Antwerp plant – couples aniline and nitrobenzene in the

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UNITED STATES INTERNATIONAL TRADE COMMISSION
Washington, D.C.

Before Paul J. Luckern
Administrative Law Judge

In the Matter of	
CERTAIN RUBBER ANTIDEGRADANTS, COMPONENTS THEREOF, AND PRODUCTS CONTAINING SAME	Inv. No. 337-TA-533

POST-HEARING BRIEF OF THE COMMISSION INVESTIGATIVE STAFF

Lynn I. Levine, Director
Jeffrey R. Whieldon, Supervisory Attorney
Juan Cockburn, Investigative Attorney

OFFICE OF UNFAIR IMPORT INVESTIGATIONS
U.S. International Trade Commission
500 E Street, S.W., Suite 401
Washington, D.C. 20436
(202) 205-2572
(202) 205-2158 (Facsimile)

December 2, 2005

of the *Graham* factors constitutes grounds for reversal of an obviousness determination. *Richardson-Vicks Inc.*, 122 F.3d at 1483-84; *Ruiz*, 234 F.3d at 660, 663-64.

Respondents contend that the asserted claims of the '063 and '111 patents are rendered obvious by the Wohl 1903 Article. RPHB at 65.

1. Scope and Content of the Prior Art

The Staff agrees with Respondents' contention that the Wohl reference discloses the only allegedly novel aspect of the patents at issue. Specifically, Wohl discloses the same starting materials and the same reaction materials to produce the same 4-ADPA intermediate products by reacting aniline and nitrobenzene with a suitable base. RPHB at 67, 70. Anticipation is avoided, however, because the asserted claims add steps whereby the 4-ADPA intermediates are converted into 4-ADPA, and/or further converted into 6PPD. Rains, Tr. 786; Beckman, Tr. 1952.

The Staff does not believe that Respondents have demonstrated that one of ordinary skill in the art would have combined Wohl with any reference because Wohl taught away from the inventions at issue. Bashkin, Tr. 2111-12

2. Secondary Considerations

The Wohl disclosure that Respondents rely upon was published in 1903. Despite its early publication, Wohl's disclosure was not used as a basis of arriving at any of the claimed inventions prior to their critical dates. The Staff believes that the foregoing is strong evidence of non-obviousness.

C. Indefiniteness Under Section 112, ¶ 2

Section 112, paragraph 2, reads as follows:

Die HHrn. Knorr und Stolz haben ihr Pikrat durch Fällen einer wässrigen Aminoantipyrinlösung mit 1-proc. wässriger Pikrinsäurelösung erhalten. Als ich mit einer mir von Hrn. Prof. Knorr in liebenswürdiger Weise überlassenen Probe von Aminoantipyrin ein Pikrat nach meiner Methode herstellte, erhielt ich ebenfalls die Substanz vom Schmp. 183—184°.

Bei der Spaltung des Condensationsproducts mit verdünnter Schwefelsäure entstehen somit Isatin und Aminoantipyrin.

696. A. Wohl: Zur Kenntniss der Reaction zwischen Nitrobenzol und Anilin bei Gegenwart von Alkali.

[Mittheilung aus dem I. Berliner Universitäts-Laboratorium.]

(Eingegangen am 23. November 1903.)

Bei der Umsetzung von Nitrobenzol mit Anilin unter Zugabe von Alkali entsteht ausser Azobenzol in beträchtlicher Menge je nach der Reactionstemperatur Phenazin, $C_6H_4\langle\overset{N}{\underset{N}{\cdot}}\rangle C_6H_4$, oder Phenazin-*N*-oxyd, $C_6H_4\langle\overset{N}{\underset{N}{\cdot O\cdot}}\rangle C_6H_4$[1]). Die Reaction wurde so erklärt, dass sich das Nitrobenzol in alkalischer Lösung zunächst in *o*-Chinonmonoxim bezw. *o*-Nitrosophenol umlagert. Bei Abwesenheit von Anilin oxydirt sich dieses, wie schon früher gefunden worden war, zu *o*-Nitrophenol[2]), bei Gegenwart von Anilin dagegen condensirt es sich mit diesem zu einem Zwischenproduct,

$$C_6H_4\langle\begin{matrix}N.OH(1)\\O(2)\end{matrix} + H_2N.C_6H_5 - H_2O =$$

$$C_6H_4\langle\begin{matrix}N.OH(1)\\N.C_6H_5(2)\end{matrix} \leftarrow C_6H_4\langle\begin{matrix}NO(1)\\NH.C_6H_5(2)\end{matrix} \rightarrow C_6H_4\langle\begin{matrix}N(OH)\\NH\end{matrix}\rangle C_6H_4,$$

das bei der Wasserabspaltung Phenazin, bei der Oxydation durch überschüssiges Nitrobenzol Phenazin-*N*-oxyd liefert.

Die Umlagerung des Nitrobenzols in *o*-Nitrosophenol wird von einer quantitativ zurücktretenden Umlagerung in *p*-Nitrosophenol begleitet, die sich bei Abwesenheit von Anilin durch die Bildung geringer Mengen *p*-Nitrophenol kennzeichnet[3]).

[1]) A. Wohl und W. Aue, diese Berichte 34, 2442 [1901].
[2]) A. Wohl, diese Berichte 32, 3486 [1899]. [3]) A. Wohl, l. c.

Es ist nunmehr gelungen auch das Product der Nebenreaction in der Pararеihe bei Anwesenheit von Anilin aufzufinden, und zwar bleibt hier, wie so häufig, das Zwischenproduct erhalten, weil im Gegensatz zur Orthoreihe die weitere Condensation unter Ringbildung nicht möglich, bezw. nicht begünstigt ist. Wird die wässrig-alkalische Lösung der Schmelze aus Nitrobenzol, Anilin und Alkali mit Kohlensäure behandelt, so erhält man in einer Ausbeute, die etwa der sonst entstehenden *p*-Nitrophenolmenge entspricht, O. Fischer's *p*-Nitrosodiphenylamin. Die Reaction verläuft also unzweifelhaft nach der Gleichung

$$C_6H_4\begin{matrix}N.OH(1)\\O(4)\end{matrix} + H_2N.C_6H_5 - H_2O$$

$$= C_6H_4\begin{matrix}N.OH(1)\\N.C_6H_5(4)\end{matrix} \rightleftarrows C_6H_4\begin{matrix}NO(1)\\NH.C_6H_5(4)\end{matrix}.$$

Oximform — Nitrosoform

Der experimentelle Nachweis, dass der Vorgang in der Pararеihe vom Nitrobenzol zu einer Verbindung der Nitrosostufe führt, bietet eine erwünschte Bestätigung für die obige Annahme eines analogen Verlaufs der Hauptreaction in der Orthoreihe. Bei dieser Gelegenheit wurde gefunden, dass das *p*-Nitrosodiphenylamin durch salzsaures Hydroxylamin in Chinondioxim übergeführt wird, nach dieser Richtung hin also jedenfalls im Sinne der obigen Oximformel $C_6H_4\begin{matrix}N.OH\\N.C_6H_5\end{matrix}$ reagirt.

30 g Anilin und 30 g Nitrobenzol werden mit 120 g fein gepulvertem, ganz trocknem Aetznatron gemischt und in einem weiten Reagensglase im Oelbade auf 110—120° erhitzt. Das Gemenge wird häufig mit einem Glasstabe umgerührt, färbt sich dann nach kurzer Zeit braun und wird beim Eintreten der Reaction zunächst dünnflüssig. Die Temperatur wird jetzt zwischen 120—125° gehalten. Hierbei beginnt die Masse bald sich dunkler zu färben, erst dickflüssig und nach einiger Zeit ziemlich hart zu werden. Wenn die Masse in diesem Zustande ist, kann man die Reaction für beendet ansehen. Das beim Erkalten vollständig hart werdende Reactionsproduct wird am besten noch heiss in ca. 1 L Wasser gebracht. Zum besseren Auslangen des Aetznatrons erwärmt man es auf einem Wasserbade und lässt es dann in einer Eismischung erkalten, bis die entstandene Base und das Azobenzol wieder krystallisirt sind. Jetzt saugt man die alkalische Flüssigkeit durch ein gehärtetes Filter ab und wäscht den festen Rückstand zur Beseitigung des an ihm noch haftenden Alkalis mehrmals mit Wasser aus. Die stark alkalische Flüssigkeit wird mit Kohlensäure behandelt. Nach etwa 2-stündigem Einleiten wird von den ausgefallenen, schwarzblauen Nadeln abfiltrirt und in das Filtrat

nochmals eine bis zwei Stunden Kohlensäure eingeleitet. Die jetzt noch ausgefällten Krystalle werden zugleich mit den zuerst erhaltenen umkrystallisirt. Die Ausbeute beträgt nach einmaligem Krystallisiren aus Alkohol 1.6 g. Reiner wird die Substanz so erhalten, dass man die alkoholische Lösung bis zur beginnenden Emulsion mit Wasser verdünnt und einige Zeit stehen lässt. Dann fallen glänzende, blauschwarz gefärbte, lange Nadeln aus, die nach nochmaligem Umkrystallisiren bei 145° (corr.) schmelzen.

0.1831 g Sbst.: 0.4878 g CO_2, 0.0842 g H_2O. — 0.1542 g Sbst.: 19.3 ccm N (24°, 760 mm).

$C_{12}H_{10}ON_2$. Ber. C 72.72, H 5.05, N 14.14.
Gef. » 72.63, » 5.12, » 13.94.

0.1101 g Substanz wurden in 16.822 g Benzol gelöst und erniedrigten den Schmelzpunkt um 0.170°. Mol.-Gew. 190 gef.; ber. für $C_{12}H_{10}ON_2$ 198.

Beim Vergleich mit dem auf andere Weise dargestellten *p*-Nitrosodiphenylamin ergab sich die völlige Uebereinstimmung der beiden Körper in Bezug auf physikalische Eigenschaften und chemische Reactionen. Das Benzoat zeigt den Schmp. 158° (corr.)[1].

Einwirkung von salzsaurem Hydroxylamin.

600 ccm Wasser wurden mit 4 g Nitrosodiphenylamin und 3.5 g salzsaurem Hydroxylamin unter beständigem Rühren zum Sieden erhitzt, bis die blauen Krystalle völlig gelöst waren. Nach Entfernung einer geringen Menge schwarzer Zersetzungsproducte schieden sich aus dem tiefrothen Filtrat beim Erkalten feine, röthliche Nadeln ab, die durch einmaliges Umkrystallisiren aus siedendem Wasser unter Zusatz von Thierkohle nahezu farblos wurden. Damit die Krystalle sich nicht in wasserhaltigem Zustande abscheiden, muss nach dem Abfiltriren von der Thierkohle die heisse, hellgelbe Lösung möglichst schnell gekühlt werden. Ausbeute 1.2 g. Beim Erhitzen der Substanz über 200° erfolgt allmähliche Zersetzung, die gegen 230—240° vollständig wird.

0.1068 g Sbst.: 0.2054 g CO_2, 0.0430 g H_2O. — 0.1284 g Sbst.: 21.7 ccm N (17°, 758.3 mm).

$C_6H_6O_2N_2$. Ber. C 52.18, H 4.35, N 20.23.
Gef. » 52.43, » 4.49, » 20.42.

Diese Zahlen liessen auf Chinondioxim schliessen. In der That stellte sich heraus, dass das erhaltene Product in seinen äusseren Eigenschaften sowohl wie in seinen Reactionen dem schon auf andere

[1]) Bridge, Ann. d. Chem. 277, 103, giebt 156° an.

Weise dargestellten und mehrfach beschriebenen Chinondioxim völlig glich.

Aus dem tiefrothen Filtrat konnte weder durch Eindunsten im Vacuum, noch durch Ausäthern, noch durch Wasserdampfdestillation ein einheitliches Product isolirt werden. Da bei der Reaction Anilin entstehen muss, das sich im Filtrat nicht nachweisen lässt, so ist anzunehmen, dass das salzsaure Anilin im Entstehungszustande sich mit einem Theil des *p*-Nitrosodiphenylamins zu Azophenin und anderen Farbstoffen umsetzt.

Darstellung der dem *p*-Nitrosodiphenylamin entsprechenden Naphtoverbindung.

20 g *α*-Naphtylamin wurden mit 17 g Nitrobenzol und 100 g gepulvertem Natronhydrat gemischt und im Oelbade auf 115—120° erhitzt, bis das Gemenge nach völliger Verflüssigung wieder fest geworden war. Das Reactionsproduct wurde dann unter gelindem Erwärmen mit einem Liter Wasser ausgelaugt, die so gewonnene alkalische Flüssigkeit ausgeäthert und Kohlensäure eingeleitet. Hierbei fielen 0.17 g eines braunen, amorphen, die Filterporen leicht verstopfenden Pulvers aus. Dasselbe wurde in Alkohol gelöst und bis zur bleibenden Emulsion mit Wasser verdünnt.

Im Verlaufe von mehreren Tagen schieden sich feine, blaue Nadeln ab, deren Aussehen sehr an das *p*-Nitrosodiphenylamin erinnerte, und die auch einen näherliegenden Schmp. (143°) zeigten. Jedoch wurde durch das Zusammenmischen beider Substanzen der Schmelzpunkt um 23° erniedrigt, wodurch bewiesen ist, dass Identität nicht besteht. Schwefelsäure löst das *p*-Nitrosodiphenylamin mit rothbrauner, das neue Product mit grüner Farbe. Auf eine Analyse desselben musste wegen der äusserst geringen Reinausbeute verzichtet werden. Doch kann man wohl annehmen, dass die dem *p*-Nitrosodiphenylamin entsprechende Naphtoverbindung vorliegt.

Wurde derselbe Versuch mit *β*-Naphtylamin ausgeführt, so blieb die alkalische Lauge bei der Behandlung mit Kohlensäure klar, desgleichen bei Anwendung von *o*-Nitrotoluol.

Die vorstehend beschriebenen Versuche sind von Hrn. W. Aue[1]) begonnen und von O. Ahlert[2]) fortgesetzt worden.

[1]) Dissert., Berlin 1902. [2]) Dissert., Berlin 1903.

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695. A. Wohl: Relating to the reaction between nitrobenzene and aniline in the presence of alkali.

[Information from the 1st Berlin University Laboratory]
(Received Nov. 23, 1903)

The conversion of nitrobenzene with aniline, with admixture of alkali, results in azobenzene as well as the following considerable amounts, depending on the reaction temperature:
phenazine,

or phenazine-N-oxide

The reaction was explained in that nitrobenzene in an alkaline solution initially rearranges itself into *o*-quinonemonoxime and/or *o*-nitrosophenol and, in the absence of aniline, oxidizes into *o*-nitrophenol[2], as was found previously. However, in the presence of aniline, it condensates therewith to form an intermediate product which supplies phenazine with the elimination of water and supplies phenazine-N-oxide during the oxidation with excess nitrobenzene.

The rearranging of the nitrobenzene into *o*-nitrosophenol is accompanied by a quantitative reduction in the rearrangement into *p*-nitrosophenol which is distinguished in the absence of aniline by the formation of small amounts of p-nitrophenol[3].

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[1] A. Wohl and W. Aue, these reports 34, 2442 [1901]
[2] A. Wohl, these reports 32, 3486 [1899]
[3] A. Wohl, l.c.

The product of the secondary reaction can also be found in the para series in the presence of aniline. As happens frequently, the intermediate product is retained in this case because, in contrast to the ortho series, the further condensation with ring formation is not possible and/or not favored. If the watery alkaline solution of the melt of nitrobenzene, aniline and alkali is treated with carbonic acid, the yield obtained corresponds approximately to the p-nitrophenol yield that otherwise develops (O. Fischer: p-nitrosodiphenylamine). The reaction without doubt follows the equation below:

The experimental proof that the reaction in the para series leads from nitrobenzene to a compound of the nitroso stage, is a desired confirmation for the above assumption of an analog course of the main reaction in the ortho series. At this opportunity, it was also found that *p*-nitroso diphenylamine is converted to quinone dioxim by means of hydrochloric acid hydroxylamine, meaning in this direction it reacts within the meaning of the above oxim formula

30 g aniline and 30g nitrobenzene are mixed with 120 g of finely pulverized, completely dry caustic soda and heated in a wide-mouth test tube in an oil bath to 110 - 120 °. The mixture is frequently stirred with a glass stirrer and, after a short time, the mixture changes to a brown color. The mixture has initially low viscosity at the start of the reaction. The temperature is held approximately in the range of 120 - 125°. The mass soon starts to become darker and more viscous and, after some time, becomes quite hard. In this state, the reaction can be considered completed. The reaction product, which becomes completely hard during the cooling down, is best placed into approximately 1l water while it is still hot. To better leach out the caustic soda, it is warmed up in a water bath and allowed to cool in an ice mixture until the resulting base and the azobenzene have recrystallized. Following this, the alkaline liquid is suctioned off through a hardened filter and the solid residue is washed several times with water to remove any alkali still clinging to it. The strong alkaline liquid is treated with carbonic acid. Following an approximately 2-hour feed-in, precipitated out dark-blue needles are filtered out and

more carbonic acid is fed in for one to two hours. The crystals which are then precipitated out are recrystallized at the same time as the first ones. The yield following a one-time crystallization from alcohol is 1.6g. A more pure substance is obtained in that the alcoholic solution is diluted with water up to the emulsion state and allowed to rest for some time. Glossy, blue-black and long needles are then precipitated out, which melt at 145° (corr.) following a second re-crystallization.

0.1831g; subst. 0.4878g CO_2; 0.0842g H_2) - 0.1542g subst.: 19.3 ccm N (24°, 760mm)

$C_{12}H_{10}ON_2$ range: C 72.72, H 5.05, N 14.14
prec.: >> 72.63 >> 5.12, >> 13.94

0.1101g substance was dissolved in 16.822g benzene, thereby lowering the melting point by 0.170°. Mol. weight 190 comp. for $C_{12}H_{10}ON_2$ 198.

A comparison with the otherwise shown *p*-nitrosodiphenylamine resulted in a complete match between the two bodies with respect to physical properties and chemical reaction. The benzoate has a melting point of 158° (corr.)[1)]

Action of Hydrochloric-Acid Hydroxylamine

An amount of 600 ccm water and 4g nitrosodiphenylamine and 3.5g hydrochloric acid hydroxylamine was heated while constantly stirred to the boiling point, until the blue crystals had dissolved completely. Following the removal of a small amount of black decomposition products, fine, red needles precipitated out of the dark red filtrate following cooling down. These needles became nearly colorless after a one-time re-crystallization in boiling water with the admixture of animal charcoal. So that the crystals do not precipitate out in the hydrous state, the hot, light-yellow solution must be cooled as quickly as possible following the removal by filtering of the animal charcoal. The yield is 1.2g. When heating the substance above 200°, a gradual decomposition takes place, which is complete near 230 - 240°.

0.1068g substance: 0.2054g CO_2, 0.0430g H_20 - 0.1234g substance: 21.7ccm N (17°, 758.3 mm)

These numbers lead to the conclusion of quinonedioxim. Indeed, it has turned out that the resulting product has external characteristics that completely

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[1)] Bridge, Ann. The Chemistry 277, 103; results in 156°

resemble in the reactions the quinonedioxim shown previously and described repeatedly.

No uniform product could be isolated out of the dark red filtrate, neither through evaporating it down in a vacuum, nor through ether extraction, nor through water-vapor distillation. Since the reaction must produce aniline, which cannot be detected in the filtrate, it must be assumed that the hydrochloric-acid aniline in the formation state converts with a portion of the *p*-nitrosodiphenylamine to form azophenin and other colorants.

Illustration of the naphto compound that corresponds to the *p*-nitrosodiphenylamine.

20g α-naphtylamine were mixed with 17g nitrobenzene and 100g powdered hydrated soda and heated in the oil bath to 115 - 120° until the mixture became completely solid again following a complete liquefying. The reaction product was leached out with one liter of water, following a slight heating, and the resulting alkaline liquid was ether extracted and carbonic acid was fed in. In the process, 0.17g of a brown, amorphous powder was precipitated out, which easily clogs the filter pores. The same was dissolved in alcohol and diluted with water up to a permanent emulsion.

During the course of several days, fine blue needles were precipitated out, the appearance of which resembled closely the *p*-nitrosodiphenylamine and which also exhibited a closer melting point (143°). Nevertheless, the mixing of the two substances lowered the melting point by 23°, thus proving that it is not identical. Sulphuric acid dissolves the *p*-nitrosodiphenylamine with the red-brown color; whereas the new product has a green color. Owing to the extremely small yield of pure substance, we had to dispense with an analysis. However, the presence of the naphto compound that corresponds to the *p*-nitrosodiphenylamine can be assumed.

When the same experiment was carried out with ß-naphtylamine, the alkaline base remained clear when treated with carbonic acid and the same was true when using *o*-nitrotoluene.

The above-described examples were started by W. Aue[1)] and were continued by O. Ahlert[2)].

[1)] Dissertation, Berlin 1902 [2)] Dissertation, Berlin 1903

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AFFIDAVIT OF ACCURACY

I, Elizabeth Meyer, hereby certify that documents bearing production numbers SCS014262-SCS014265 are, to the best of my knowledge and belief, a true and accurate translation of A. Wohl, Zur Kenntniss de Reaction zwischen Nitrobenzol und Anilin bei Gegenwart von Alkali, Chemische Berichte, 36:4135-4138 (1903), from German to English.

Elizabeth Meyer
TransPerfect Translations
601 Thirteenth Street, NW
Suite 320 North
Washington, DC 20005

Sworn to before me this
7th day of October, 2005

Signature, Notary Public

Lisa Sherfinski
Notary Public, District of Columbia
My Commission Expires 01-01-2008

Stamp, Notary Public

District of Columbia